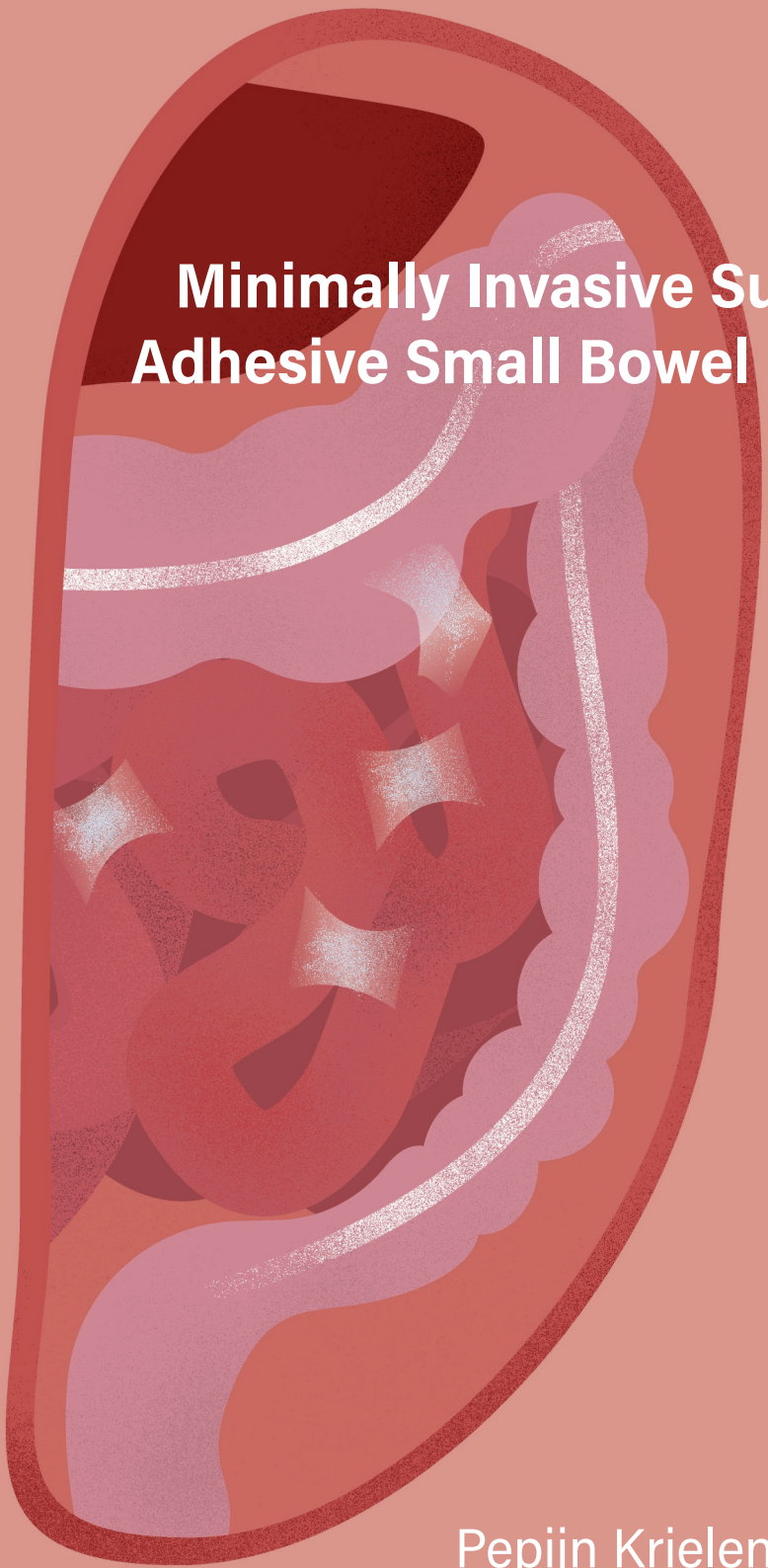

# Minimally Invasive Surgery and Adhesive Small Bowel Obstruction

Pepijn Krielen

# MINIMALLY INVASIVE SURGERY AND ADHESIVE SMALL BOWEL OBSTRUCTION

**Pepijn Krielen**

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# Minimally invasive surgery and adhesive small bowel obstruction

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to obtain the degree of doctor
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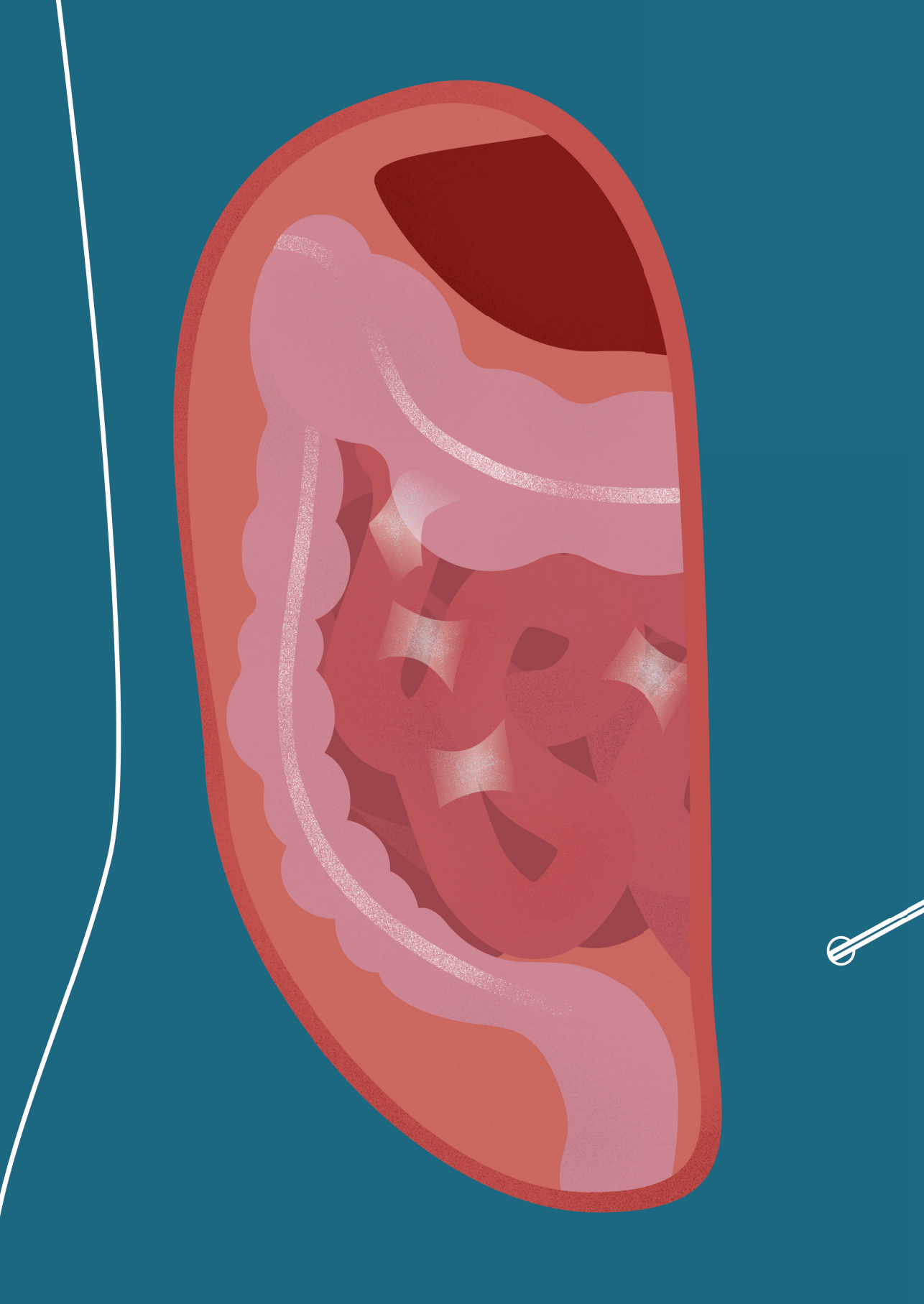
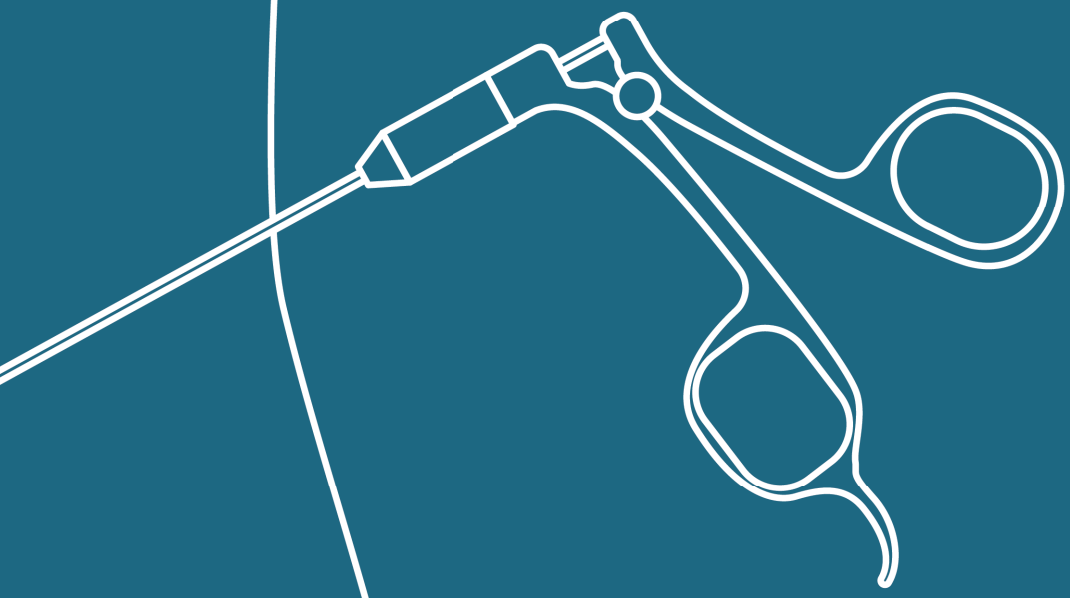


# 1

# Introduction



## 1. Adhesion formation in the minimal invasive era

Adhesions are filmy or dense scar tissues which develop between intra-abdominal organs and the abdominal wall after peritoneal trauma. Abdominal surgery is the main contributor to peritoneal trauma. Over 90% of patients develop adhesions after open surgery, and 45-62% do so after minimally invasive surgery.[1-4] Other precipitants of adhesion formation include intra-abdominal infections, tumors and radiotherapy.[5] Adhesions impart tremendous clinical and economic burdens, carrying a life-long risk of adhesion-related complications, including adhesive small bowel obstruction (ASBO), female infertility, chronic visceral pain, and difficulties during reoperations.[6] ASBO is a surgical emergency in which the obstruction of the small intestine hinders passage of intestinal contents, which may necessitate an emergency reoperation to resolve the obstruction. During reoperations, the need to cut adhesions in order to gain access to the operative area creates a risk of iatrogenic injuries to organs and structures, particularly to the bowel. The incidence of iatrogenic bowel injury during reoperation is estimated to be 6%, resulting in an increase in post-operative complications including sepsis and surgical site infections, as well as increased mortality.[7] The Surgical and Clinical Adhesion Research (SCAR) study, published two decades ago, was the first population-based study to report incidence rates of adhesion-related readmissions. One in three patients was found to be readmitted after abdominal surgery for a cause possibly related to adhesions.[4] With the publication of this study surgeons and researchers became more aware of the magnitude of the problem of adhesions, resulting in increased attention to adhesion reduction strategies.

In the same decade, there was a rapid growth of minimally invasive operations. Through its peritoneal tissue sparing character and minimal blood loss, laparoscopy was soon claimed to reduce adhesion formation and associated complications. Consequently, surgeons started to advocate laparoscopic surgery as the most relevant adhesion reduction strategy.[8] At present, the laparoscopic approach has replaced open surgery as the standard of care for a wide spectrum of intra-abdominal procedures. In the Netherlands, over 75% of all colorectal procedures are performed laparoscopically.[9] Indications for laparoscopic surgery are rapidly expanding in recent years, for example, esophagectomy and hepato-pancreato-biliary (HPB) surgery have increasingly transitioned to laparoscopic approaches. The

introduction of laparoscopy, however, is still is considered potentially hazardous for a small number of procedures, such as Whipple procedures.[10]

Several studies have reported a reduction in adhesion extent and severity after minimally invasive surgery.[2,3] However, it is unknown whether a reduction in adhesion formation will result in a proportionate decrease in the rate of adhesion-related complications. For example, ASBO can be caused either by extensive dense abdominal adhesions or by even a single adhesive band. Studies on the risk of ASBO after minimally invasive surgery report conflicting evidence.[6,11] The primary reason is that most trials on minimally invasive surgery are not designed and powered for adhesion formation, let alone specific long-term complications such as ASBO.

Further complicating the topic of adhesion-related morbidity after minimally invasive surgery are differences in definitions and management of ASBO reported between different studies. ASBO is often defined as an episode of small bowel obstruction (SBO) with operative confirmation of adhesions. However, adhesions cannot be confirmed as the cause of the SBO when it is treated by conservative (i.e. non-operative) means. Thus, the true incidence of ASBO may be substantially underestimated using a definition that relies on operative visualization. A second definition of ASBO is an episode of SBO suspected to be related to adhesions via radiological imaging, excluding other potential causes of SBO, such as a groin hernia or a tumor. The incidence determined under this definition is affected by the portion of patients who have imaging upon diagnosis, the timing of imaging in the disease course, and the imaging modality.[12-14] The limitations of both definitions make it difficult to truly compare different studies' results on the incidence of ASBO and re-ASBO, after both minimally invasive and open surgery.

The lack of reliable data on the risk of ASBO and other adhesion-related complications after minimally invasive surgery not only jeopardizes daily practice; it also paralyzes initiatives to develop and introduce new and current adhesion reduction strategies. To stimulate progress in this field, it is essential to collect and analyze big epidemiological data on the risk of adhesion-related complications after minimally invasive surgery.

**2. Burden of adhesive small bowel obstruction**

Adhesions are known to cause over 55% of all episodes of SBO.[6] Morbidity associated with ASBO is high, resulting in an average of 7.8 days hospital admission and in-hospital mortality of 2.5%.[6] The incidence of ASBO in the first years after abdominal surgery is estimated at 2-3%.[6] ASBO risk varies depending on the location of the inciting surgery, from 0.5 percent in abdominal wall surgery to 3.2 percent in lower gastro-intestinal tract surgery.[6] Recent reports on emergency surgery in the UK and USA show that ASBO is a major contributor to morbidity, mortality, and costs. In 2016, 51% of all emergency laparotomies in the UK were for ASBO.[15] In the USA between 2008 and 2011, adhesiolysis for SBO ranked among the top five most common emergency surgical procedures.[16] Associated health care costs are likely much higher than reported, as most studies on the costs of ASBO only include (incomplete) in-hospital costs or cost based on reimbursement prices.[17,18]

Despite the high incidence of ASBO and its associated morbidity, treatment of ASBO is mostly determined by personal preferences of physicians rather than evidence-based protocols. Many recommendations set forth by existing guidelines are based on low-quality and/or conflicting evidence. Patient characteristics and disease parameters that indicate a need for operative treatment are not specific, and the choice of operative treatment depends largely upon the judgement of the consulting surgical team.

Operative management of ASBO historically consists of adhesiolysis by open surgery. The primary immediate drawback of operative ASBO management is the risk of iatrogenic bowel injury due to a severely distended and vulnerable bowel.[7] Due to repeat peritoneal trauma imparted by open surgery for ASBO, lysed adhesions reform, an new adhesions form at other injured areas in the peritoneal cavity, risking a new episode of ASBO and inciting a potentially vicious cycle.

Given the risk of exacerbating peritoneal trauma, it is considered an advantage that more than 70 to 90 percent of all episodes of ASBO are managed non-operatively with gastric decompression, fluid resuscitation, and nil per os.[6,19,20] However, while conservative management may ease a particular episode of SBO, the offending underlying adhesions are not resolved, which means that the risk of a new episode of ASBO persists indefinitely. After

a first episode of ASBO, the risk of recurrence was found lower after operative management compared with non-operative management (13% vs. 21% after a median of 3.6 years follow-up).[21,22] When an ASBO recurs, the time interval between episodes tends to decrease with every new episode.[21] Despite the long-term lower risk of recurrence of ASBO after adhesiolysis, a trial of non-operative management is recommended by the guidelines, trying to avoid the immediate complications of surgical intervention.[23]

In cases where a decision is made to proceed operatively, the next important question is whether a laparoscopic approach to ASBO is more effective compared with open adhesiolysis. Laparoscopic surgery may not only prevent formation of new adhesions, but also adhesion reformation and formation at other areas. Over the past several decades, a few case series of laparoscopic treatment of ASBO have been described.[24] Early adopters have emphasized the advantages of a minimally invasive approach to ASBO, including reduced post-operative length of stay, improved gastro-intestinal recovery, and minimal wound problems. However, long-term benefits have not been substantiated and compared with results from open adhesiolysis. Critics of laparoscopic adhesiolysis for ASBO draw attention to the small laparoscopic working space, the increased risk of iatrogenic bowel perforations in case of a severely extended bowel, and the selected “easy” operative cases included in the series.[25] Selection criteria to indicate which patient may benefit the most of laparoscopic surgery for ASBO, and which red flags should demand open surgery, are important questions for researchers to address.

In this thesis, I will comprehensively assess the existing literature on management of ASBO, with a particular focus on the proper role of minimally invasive surgery, to provide treatment recommendations based upon the best available evidence to date.

**3. Adhesion prevention in contemporary surgery**

Aside from ‘optimal surgical technique’, a predominant means of preventing adhesion formation is the intraoperative application of an adhesion barrier at the end of a surgical procedure. Most barriers are bioresorbable films, sprays, viscous gels, and liquids, which

are intended to separate peritoneal wound surfaces until adhesion-free wound healing can occur. Studies on adhesion barriers have proven these devices to be safe and effective.[26] This evidence is mainly derived from trials in open surgery. Yet despite the evidence, barriers have not been widely adopted by the surgical community. An important factor limiting broad use of barriers is doubt about their cost-effectiveness, as well as lack of reimbursement in many countries, burdening hospitals with the marginal increase in expense.

Today, a vast majority of surgical procedures are routinely performed through minimally invasive means. In 2010, only 13 percent of Dutch surgeons indicated they had used an adhesion barrier in the previous year.[27] Adhesion barriers were said to be superfluous due to a strong belief in the adhesion prevention potential of minimally invasive techniques. In contrast, opinion leaders in adhesion prevention have highlighted the use of adhesion barriers in minimally invasive surgery, showing evidence of adhesion-related complications after major gynecological and general laparoscopic surgery.[4,28] However, hindering the fight for adhesion prevention in minimally invasive surgery is the fact that most barriers on the market were developed and studied in open surgical settings, as opposed to minimally invasive surgery. For example, film barriers are difficult to handle in laparoscopic surgery; they cannot pass through a trocar, they are challenging to unroll or fragment, and they are difficult to place at the desired location due to rapid adhesiveness when they come into contact with fluid. Icodextrin (Adept®, Baxter, Deerfield, IL, USA) was developed to be used in open and laparoscopic surgery; however, it has only been approved for a limited number of benign gynecological laparoscopic operations.[29]

Solid evidence of adhesion barriers' cost-effectiveness in preventing adhesion-related complications is key to progressing with next steps in adhesion prevention and reimbursement of barriers, both in open and minimally invasive surgery. Previous studies on cost-effectiveness made use of incomplete cost estimations, and only included direct cost savings for the prevention of ASBO, not taking in to account other common complications of adhesions such as difficulties during reoperations. Furthermore, costs in these studies were often derived from reimbursement data rather than true healthcare costs.

In this thesis I will assess healthcare costs from ASBO using micro-costing methods to provide a more accurate estimate of the true financial burden of ASBO on healthcare systems. This analysis will form a firm basis for a cost-effectiveness study on the routine use of adhesion barriers in procedures with a high risk of adhesion formation, such as colorectal surgery. Outcomes may serve to increase surgeons' awareness of the importance and cost-effectiveness of adhesion prevention, when performing open or minimally invasive operations in the peritoneal cavity.

Interest in adhesion prevention and barrier use may also be stimulated through better understanding of the impact of intra-operative adhesiolysis on post-operative morbidity. The necessity to lyse adhesions during repeat surgery delays the main operation and imparts an increased risk of post-operative complications. Previous studies have showed an increase in mortality (OR 5.19), sepsis (OR 5.12), intra-abdominal complications (OR 3.46), wound infections (OR 2.45), hospital stay (2.06 ± 1.06 days) and hospital costs ($18.600 compared with $14.000 in surgery without adhesiolysis) in case of adhesiolysis during reoperations.[7,30] Despite these unfavorable outcomes, many surgeons do not recognize the relationship between intra-operative complications associated with adhesiolysis and adverse post-operative outcomes. This is partly explained by the lack of consensus regarding the severity of intra-operative adverse events.

Recently, a scoring system of intra-operative adverse events has been validated for all types of surgeries.[31] In this thesis, I will determine the inter-rater agreement of the Classification of Intra-operative Adverse Events (ClassIntra®), and its predictive value on post-operative complications in a cohort of abdominal surgeries, with specific interest in adhesiolysis-related complications.

**Objectives of this thesis**

The first objective is to delineate the impact of minimally invasive surgery on adhesion-related complications on a population level.

The secondary objective is to increase the evidence base regarding the treatment of ASBO, discussing the optimal treatment while taking into account the advent of widespread laparoscopic adhesiolysis.

The third objective is to increase awareness of the importance of adhesion prevention in contemporary surgery in the peritoneal cavity through improved mapping of intra-operative and post-operative adverse events, and demonstration of the cost-effectiveness of adhesion barriers in open and laparoscopic surgery.

**Outline of this thesis**

In **Chapter 2**, the impact of minimally invasive surgery on adhesion-related readmissions is assessed in a population based cohort study. While minimally invasive surgery reduces adhesion formation, it is unknown whether a reduction in adhesions leads to a proportionate reduction in adhesion-related complications needing readmissions. Data is collected on adhesion-related readmissions after open and minimally invasive abdominal or pelvic surgery from a large established Scottish registry database. The results of this study will provide insight into the burden of adhesions due to minimally invasive surgery, and the need and the magnitude of future adhesion prevention measures.

In **Chapter 3**, detailed information on the impact of laparoscopic colorectal surgery on adhesion-related readmissions is gathered in a subgroup of the population-based cohort described in chapter 2. The colorectal subgroup represents a large proportion of abdominal surgeries, and harbors the highest risk of adhesion formation and adhesion-related complications. Furthermore laparoscopy has become the modality of choice in colorectal surgery in many high-income countries.

In **Chapter 4**, recent literature is reviewed concerning the diagnosis and treatment of ASBO, inclusive of minimally invasive approaches. Since both radiological imaging techniques and operative techniques have improved in recent years, an update of the current Bologna guideline on treatment of ASBO was considered to be necessary. New and better evidence is presented for both diagnosis and management of ASBO, with practical recommendations provided. It is anticipated that diagnosis and treatment will improve for the individual patient with ASBO, independent from treating physician´s preferences and local resources.

In **Chapter 5**, the current literature is systematically reviewed and meta-analyzed regarding minimally invasive and open surgery for ASBO. Minimally invasive surgery may reduce peritoneal wound surfaces, thereby theoretically resulting in fewer reformed adhesions, in addition to the general post-operative advantages such as decreased pain, faster gastro-intestinal recovery, and minimal wound problems. However, due to a small working space as a result of distended bowels, concerns are raised for an increase in iatrogenic bowel perforations associated with the laparoscopic approach. The results of this review may assist surgeons in making evidence-based decisions concerning the optimal operative approach to a patient with ASBO, while taking into account both early and long-term post-operative consequences.

In **Chapter 6**, the inter-rater agreement of the newly proposed ClassIntra® score for intra-operative adverse events and its predictive value for post-operative complications is assessed. ClassIntra® defines all deviations from the ideal intra-operative course as an adverse event, and has been validated in a large prospective series of all-type surgeries. However, in this validation, the impact of the type of intra-operative complication was not assessed. In previous studies, our research group demonstrated that the specific type of adhesiolysis-associated intra-operative complication had clinical significance; for example, a bowel serosal injury versus a bowel perforation. In this study, the ClassIntra® score has been applied to a dataset of patients who have had elective abdominal (re-)surgery, and whose adhesiolysis-associated intra- and post-operative complications have been documented in a rigorous prospective way.[7] Results of this study will be valuable regarding uniform scoring of adverse events in abdominal surgery, and the awareness that adhesiolysis-related adverse events have direct consequences for post-operative recovery.

In **Chapter 7**, a detailed cost analysis of ASBO admissions is performed. In 39 consecutive cases of ASBO, hospital costs are calculated using micro costing methods. Costs are presented for operative and non-operative management of ASBO separately. Results of this study will provide a greater insight regarding when and how to introduce adhesion prevention means.

In **Chapter 8**, a decision tree model is constructed to model the cost-effectiveness of the routine use of adhesion barriers in open and minimally invasive colorectal surgery on adhesions and ASBO, based on the best available evidence. There is a gap between evidence of barriers' clinical effectiveness and their clinical use, which is attributed to prior equivocal reports on barriers' cost-effectiveness. For laparoscopic surgery, limited information of this sort was previously available. Results of this study will help both surgeons and policy makers both inside and outside the hospital to develop a substantiated program of (routine) adhesion prevention in open and laparoscopic colorectal surgery.

In **Chapter 9**, I will discuss minimally invasive surgery in the context of adhesive bowel obstruction, addressing the findings of the studies in this thesis and those of existing literature.

In **Chapter 10**, a summary of the chapters of this thesis is presented, and a perspective regarding future research avenues on the topic of "adhesions in the minimally invasive era" is outlined.

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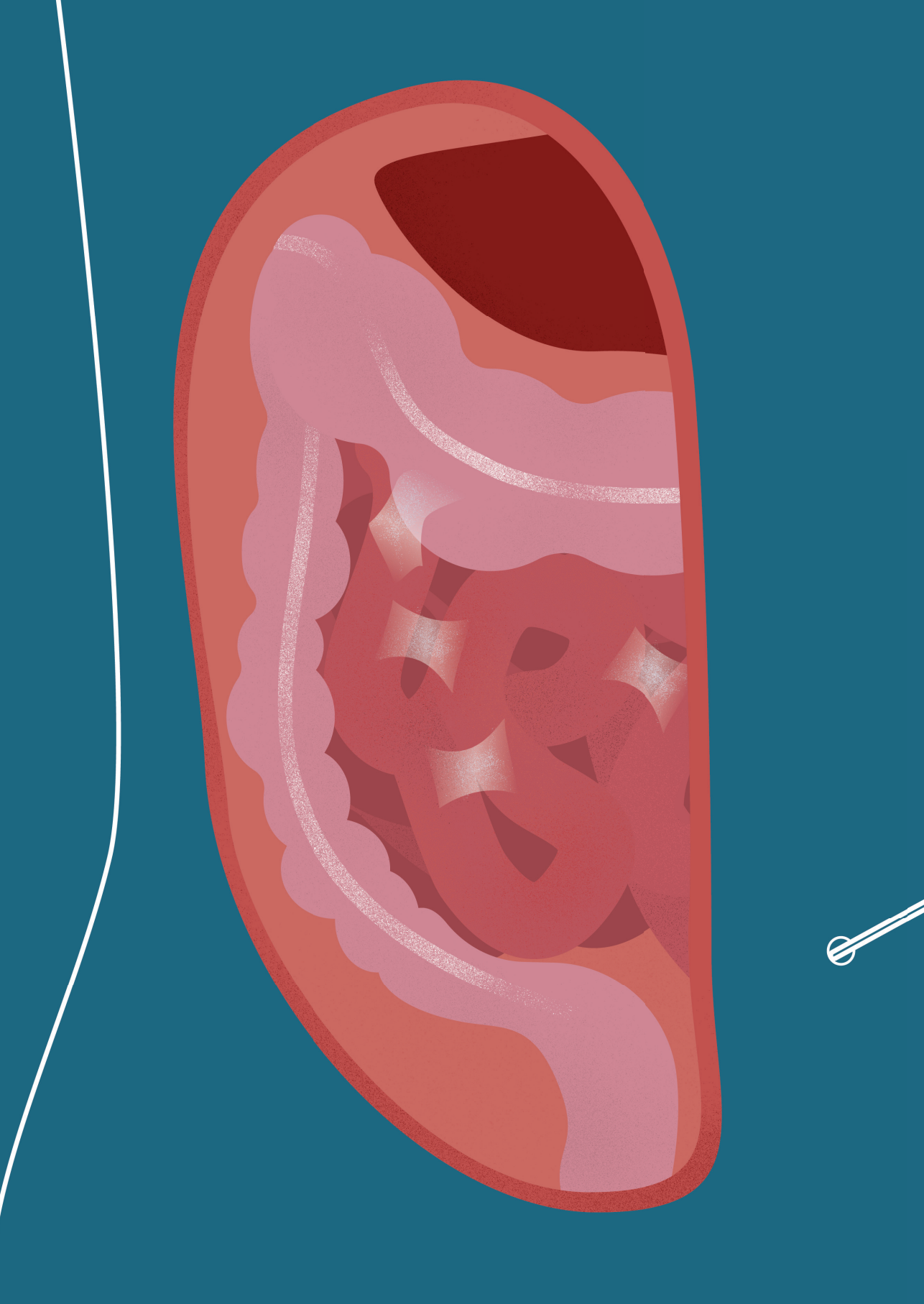
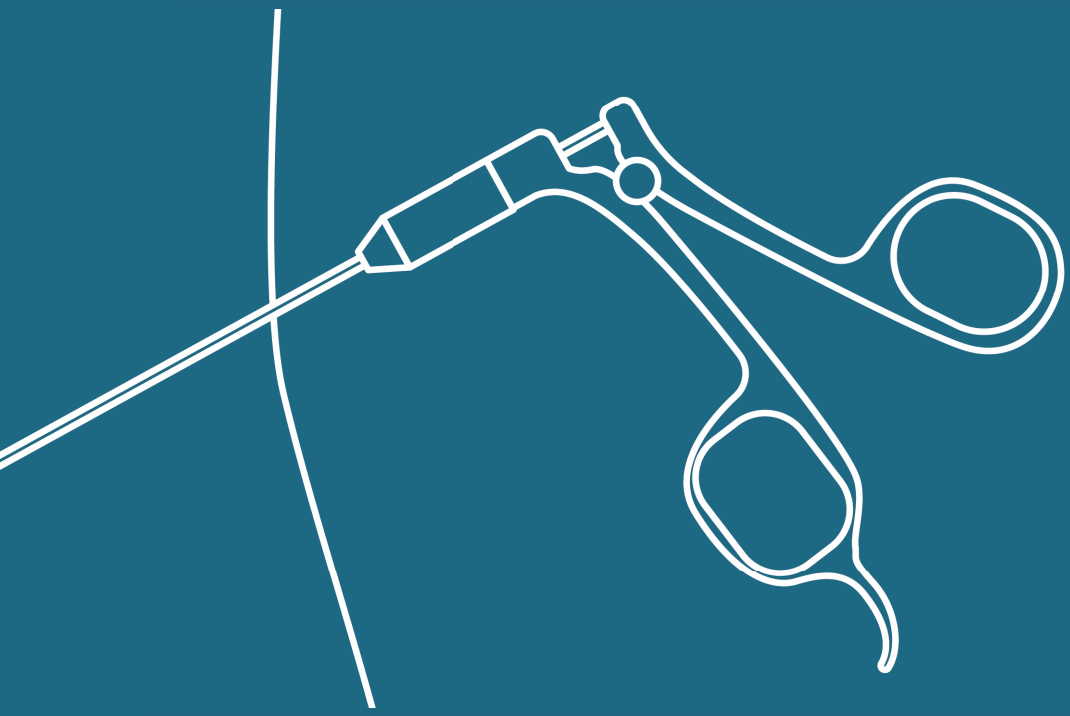


# 2

# Adhesion-related readmissions after open and laparoscopic surgery: a retrospective cohort study (SCAR update)



Pepijn Krielen, Martijn W.J. Stommel, Pille Pargmae, Nicole D. Bouvy, Erica Bakkum, Howard Ellis, Mike C. Parker, Ewen A. Griffiths, Harry van Goor, Richard P.G. ten Broek

Lancet 2020 Jan 4;395(10217):33-41

**Abstract**

*Background*

Adhesions are the most common driver of long-term morbidity after abdominal surgery. Although laparoscopy can reduce adhesion formation, the effect of minimally invasive surgery on long-term adhesion-related morbidity remains unknown. We aimed to assess the impact of laparoscopy on adhesion-related readmissions in a population-based cohort.

*Methods*

We did a retrospective cohort study of patients of any age who had abdominal or pelvic surgery done using laparoscopic or open approaches between June 1, 2009, and June 30, 2011, using validated population data from the Scottish National Health Service. All patients who had surgery were followed up until Dec 31, 2017. The primary outcome measure was the incidence of hospital readmissions directly related to adhesions in the laparoscopic and open surgery cohorts at 5 years. Readmissions were categorised as directly related to adhesions, possibly related to adhesions, and readmissions for an operation that was potentially complicated by adhesions. We did subgroup analyses of readmissions by anatomical site of surgery and used Kaplan-Meier analyses to assess differences in survival across subgroups. We used multivariable Cox-regression analysis to determine whether surgical approach was an independent and significant risk factor for adhesion-related readmissions.

*Findings*

Between June 1, 2009, and June 30, 2011, 72 270 patients had an index abdominal or pelvic surgery, of whom 21 519 (29·8%) had laparoscopic index surgery and 50 751 (70·2%) had open surgery. Of the 72 270 patients who had surgery, 2 527 patients (3·5%) were readmitted within 5 years of surgery for disorders directly related to adhesions, 12 687 (17·6%) for disorders possibly related to adhesions, and 9 436 (13·1%) for operations potentially complicated by adhesions. Of the 21 519 patients who had laparoscopic surgery, 359 (1·7% [95% CI 1·5–1·9]) were readmitted for disorders directly related to adhesions compared with 2 168 (4·3% [4·1–4·5]) of 50 751 patients in the open surgery cohort ($p<0·0001$). 3 443 (16·0% [15·6–16·4]) of 21 519 patients in the laparoscopic surgery cohort

were readmitted for disorders possibly related to adhesions compared with 9 244 (18·2% [17·8–18·6]) of 50 751 patients in the open surgery cohort (p<0·005). In multivariate analyses, laparoscopy reduced the risk of directly related readmissions by 32% (hazard ratio [HR] 0·68, 95% CI 0·60–0·77), and of possibly related readmissions by 11% (HR 0·89, 0·85–0·94) compared with open surgery. Procedure type, malignancy, sex, and age were also independently associated with the risk of adhesion-related readmissions.

*Interpretation*

Laparoscopic surgery reduces the incidence of adhesion-related readmissions. However, the overall burden of readmissions associated with adhesions remains high. With further increases in the use of laparoscopic surgery expected in the future, the effect at the population level might become larger. Further steps remain necessary to reduce the incidence of adhesion-related postsurgical complications.

**Introduction**

Adhesions are one of the most important drivers of long-term complications in contemporary abdominal surgery.[1–4] Adhesions develop in 79–90% of patients who have open abdominal or pelvic surgery.[5–7] The original Surgical and Clinical Adhesions Research (SCAR) study,[3] published in 1999, was the first large epidemiological study to assess the morbidity and clinical impact of adhesions. In the 10 years after open surgery, approximately one in three patients were readmitted to a hospital for causes possibly related to adhesions and 5·7% of patients were admitted for causes directly related to adhesions. The landmark papers published after the subsequent colorectal and gynaecological SCAR studies contributed substantially to increased awareness of the impact of adhesion-related complications.[8,9]

A number of surgical practice reforms have occurred in the two decades since publication of the SCAR study, several of which might have contributed to reductions in post-surgical adhesions. The two most prominent developments have been the increased use of minimally invasive surgery (eg, laparoscopy) and the use of anti- adhesion barriers. During the original SCAR study period, use of laparoscopy was mostly limited to diagnostic procedures, whereas a wide range of complex procedures are now commonly done laparoscopically, such as colorectal resections. At present, adhesion barriers are rarely used, despite high quality evidence for their efficacy in reducing adhesion formation.[10,11] By contrast, laparoscopic surgery has now been widely adopted, mainly because of benefits such as reduced postoperative pain and improved cosmetic results.[12] Laparoscopic surgery reduces the extent and severity of adhesion formation by roughly 50%, mostly at the incision line.[5,13] Reduction of adhesion formation does not necessarily correlate with a proportional reduction in the risk of adhesion-related complications; a single adhesive band can sometimes cause a life-threatening bowel obstruction, whereas extensive dense abdominal adhesions might be asymptomatic.[14] Several studies have suggested that laparoscopic surgery might also be associated with a lower incidence of adhesion-related complications.[1,5] However, adhesion-related complications are often only measured as a secondary, underpowered endpoint.[15] Thus, it remains unknown whether changes in surgical practice since publication of the SCAR studies have affected the overall population

burden of adhesion formation and adhesion-related complications. In this study, we aimed to assess the incidence of adhesion-related readmissions at the population level after open and laparoscopic surgery, using comparable methods to those applied in the original SCAR studies.



## Methods

*Data sources and study population*

We did a retrospective cohort study using validated data from the Scottish Medical Record Linkage Database, managed by the National Health Service (NHS) Scotland. The database contains records for all inpatient and day- case hospital admissions in Scotland, excluding maternity and psychiatry admissions. Data from the NHS are validated annually at the hospital level by comparing 1% of local hospital clinical data with centrally held data.[16] The database has been described in detail previously.[2,3]

We included all patients of any age who had initial abdominal or pelvic surgery between June 1, 2009, and June 30, 2011, to ensure a follow-up period of 5 years. Patients with a previous history of pelvic or abdominal surgery were excluded. All patients who had surgery were followed up until Dec 31, 2017. Migration data and deaths in the cohort were also extracted.

*Procedures*

We used the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) codes to identify operation types and approaches. All operations were classified as open or laparoscopic according to OPCS-4 codes. Some OPCS-4 codes incorporated laparoscopic approaches in their original coding (eg, Q48·3, laparoscopic oocyte recovery); in most other cases, laparoscopic operations could be identified by the use of an additional code for laparoscopic surgery (eg, Y50·8, laparoscopic approach to abdominal cavity). All operations with an OPCS-4 code incorporating

laparoscopic approaches or identified by the use of an additional code for laparoscopic surgery were coded as laparoscopic.

We identified hospital readmissions using OPCS-4 codes and International Classification of Diseases, tenth edition (ICD-10) codes. Consistent with previous SCAR methods,[2,3] all readmissions were screened for their possible association with adhesions. All potentially relevant readmissions were classified as readmission directly related to adhesions (eg, adhesiolysis, adhesive small bowel obstruction); readmission possibly related to adhesions (eg, unspecified small bowel obstruction); or readmission with reoperation that could potentially be complicated by adhesions (eg, right hemicolectomy after appendectomy). We classified the association between readmissions and adhesions using relevant OPCS-4 and ICD-10 codes. Readmissions were only included in one of three categories. We excluded readmissions from analyses that were unlikely to be associated with adhesions. Only readmissions with an explicit reference to adhesions in the ICD-10 or OPCS-4 coding were classified as directly related.

Consistent with the methods of previous SCAR studies,[2,3] subgroup analyses were done by anatomical site: midgut and hindgut (small intestine, abdominal wall, appendix, rectum, colon), foregut and other abdominal organs (stomach, gallbladder, pancreas, kidney, bladder), and the female reproductive tract. Additionally, we introduced a new anatomical site classification to enable better comparison between laparoscopic and open surgeries. We compared readmission rates between open and laparoscopic surgeries for ten categories of frequent surgical procedures that comprise more than 80% of all surgical procedures. Common surgical procedures were categorised as appendectomy, cholecystectomy, procedures on the colon, rectum, liver, or upper gastrointestinal tract, urological, gynaecological procedures without uterus extirpation, gynaecological procedures with uterus extirpation, retroperitoneal surgeries, or other. Procedures were classified such that each patient would only be included in one category. For patients who were eligible for inclusion in more than one category, patients were assigned to the procedure category with the highest risk for readmissions directly related to adhesions.

*Outcomes*

The primary outcome measure was the incidence of hospital readmissions directly related to adhesions in the open and laparoscopic surgery cohorts at 5 years. Our secondary outcome measure was the incidence of possibly related readmissions. In the analysis of readmissions possibly related to adhesions, the incidence of first directly or possibly related readmissions was recorded. Additional outcome measures were annual cumulative readmission rates, association between index procedure anatomical location and adhesion-related readmissions, and association between indication for index surgery and adhesion-related readmissions. All outcome measures were analysed collectively for the overall cohort and separately for patients with open and laparoscopic index surgeries.

*Statistical analysis*

We used Kaplan-Meier analyses to assess differences in survival for all subgroups. The log-rank test was used to determine significant differences in survival between the subgroups. Multivariable survival analyses were done using Cox-regression analysis, to determine if the approach to the abdominal and pelvic cavity was an independent and significant risk factor for adhesion-related readmissions. Any independent variables associated with the dependent variables in the univariate analyses ($p<0{\cdot}2$) were entered into the multivariate analyses. Multivariable analyses were done using backward selection. Descriptive statistical analyses were done using SPSS software (version 22.0). Univariate and multivariate survival analyses were done using R (version 3.5.1). A p value of less than 0·05 was considered to indicate a statistically significant difference.

**Results**

Between June 1, 2009, and June 30, 2011, 72 270 patients had an index abdominal or pelvic surgery. 21 519 (29·8%) patients had laparoscopic surgery, which was converted to open surgery in 1822 (8·5%) patients. Table 1 shows the baseline characteristics of both cohorts. Clinically relevant differences were identified in the distribution of surgical procedures between groups. Overall, 19 278 patients (26·7%) were readmitted on 33 599 discrete

**Table 1** Demographics of study population

| | Total | Open | Laparoscopy |
|---|---|---|---|
| Patients | 72 270 | 50 751 | 21 519 |
| Admissions | 111 942 | 80 959 | 30 983 |
| Sex | | | |
| Male | 23 334 (32·3%) | 16 577 (32·7%) | 6 757 (31·4%) |
| Female | 48 934 (67·7%) | 34 172 (67·3%) | 1 4761 (68·6%) |
| Age (years) | | | |
| Range | 0* - 101 | 0* - 101 | 0* - 98 |
| Mean | 50 | 51 | 47 |
| Follow-up (months) | | | |
| Min | 0$ - 95·1 | 0$ - 95·1 | 0·2 - 91·4 |
| Mean | 70·2 | 68·4 | 74·5 |
| Operation level | | | |
| Foregut or other | 29 804 (41·2%) | 15 383 (30·3%) | 14 421 (67·0%) |
| Mid- or hindgut | 24 088 (33·3%) | 18 754 (37·0%) | 5 334 (24·8%) |
| Female reproductive tract | 18 378 (25·4%) | 16 614 (32·7%) | 1 764 (8·2%) |
| Common surgeries | | | |
| Liver | 415 (0·6%) | 325 (0·6%) | 90 (0·4%) |
| Retroperitoneal | 1 827 (2·5%) | 1 746 (3·4%) | 81 (0·4%) |
| Urologic | 3 708 (5·1%) | 2 737 (5·4%) | 971 (4·5%) |
| Upper GI | 2 777 (3·8%) | 1 838 (3·6%) | 939 (4·4%) |
| Cholecystectomy | 14 177 (19·6%) | 2 114 (4·2%) | 12 063 (56·1%) |
| Appendectomy | 7 385 (10·2%) | 4 115 (8·1%) | 3 270 (15·2%)n |
| Gynaecological | | | |
| No uterus extirpation | 10 080 (13·9%) | 8 657 (17·1%) | 1 423 (6·6%) |
| Uterus extirpation | 7 641 (10·6%) | 7 342 (14·5%) | 299 (1·4%) |
| Rectum | 3 270 (4·5%) | 2 913 (5·7%) | 357 (1·7%) |
| Colon | 5 869 (8·1%) | 5 041 (9·9%) | 828 (3·8%) |
| Other | 15 121 (20·9%) | 13 923 (27·4%) | 1 198 (5·6%) |
| Diagnosis (index admission) | | | |
| Malignancy | | | |
| Foregut and other | 4 148 (5·7%) | 3 266 (6·4%) | 882 (4·1%) |
| Mid- or hindgut | 5 420 (7·5%) | 4 608 (9·1%) | 812 (3·8%) |
| Female reproductive tract | 1 992 (2·8%) | 1 814 (3·6%) | 178 (0·8%) |
| Crohn's disease | 766 (1·1%) | 687 (1·4%) | 79 (0·4%) |
| Diverticulitis | 607 (0·8%) | 587 (1·2%) | 20 (0·1%) |

* cohort consists of all patients undergoing abdominal or pelvic surgery, including paediatric cases, $ patients with zero months follow-up died or moved out before the first month of follow-up was completed

occasions (mean 1·7 times [SD 1·7]) during the 5-year follow-up for any cause related to adhesions.

Overall, 2 527 (3·5%) of 72 270 patients were readmitted a total of 3 442 times for a cause directly related to adhesions, with a mean of 1·4 readmissions per patient [SD 0·9] during the 5-year period. 2 168 (4·3% [95% CI 4·1–4·5]) of 50 751 patients were readmitted at least once for a disorder directly related to adhesions in the open surgery cohort (mean number of readmissions 1·4 [SD 0·9]) compared with 359 (1·7% [1·5–1·9]) of 21 519 patients in the laparoscopic surgery cohort (mean number of readmissions 1·3 [0·6]), and this difference was statistically significant (p<0·0001; figure A). During the total follow-up period (mean follow-up 70·2 months), 2 314 (57·5%) of 4 021 directly related readmissions were for adhesive small bowel obstruction, 917 (39·6%) of which were treated surgically. All readmissions directly related to adhesions by anatomical site of index surgery during the full study period (mean follow-up 70·2 months) are shown in table 2.

In the 5 years after index surgery, 12 687 (17·6%) of 72 270 patients were readmitted a total of 21 778 times for a cause possibly related to adhesions, with a mean of 1·7 readmissions per patient (SD 1·8). In the open surgery cohort, 9 244 (18·2%; 95% CI 17·8–18·6) of 50 751 patients were readmitted for a cause possibly related to adhesions, with a mean 1·7 readmissions per patient (SD 1·9). In the laparoscopic surgery cohort, readmissions were lower, with 3 443 (16·0%; 95% CI 15·6–16·4) of 21 519 patients readmitted at a mean rate of 1·7 readmissions per patient (SD 1·6; p<0·0001; figure B). The diagnostic codes for possibly related readmissions did not differ between the open and laparoscopic surgery cohorts. The most frequent causes of readmission were abdominal or pelvic pain, change in bowel habits, nausea, and vomiting (appendix p 1).

Overall, 9 436 (13·1%) of 72 270 patients were readmitted a total of 11 821 times for reoperations potentially complicated by adhesions, with a mean of 1·3 reoperations per patient (SD 0·7) recorded during the 5-year period after surgery. Reoperations were done laparoscopically in 1 572 (13·3%) of 11 821 reoperations. Patients in the laparoscopic surgery cohort were less frequently readmitted for reoperations potentially complicated by adhesions than patients in the open surgery cohort (1 844/21 159 [8·6%; 95% CI 8·2–9·0]

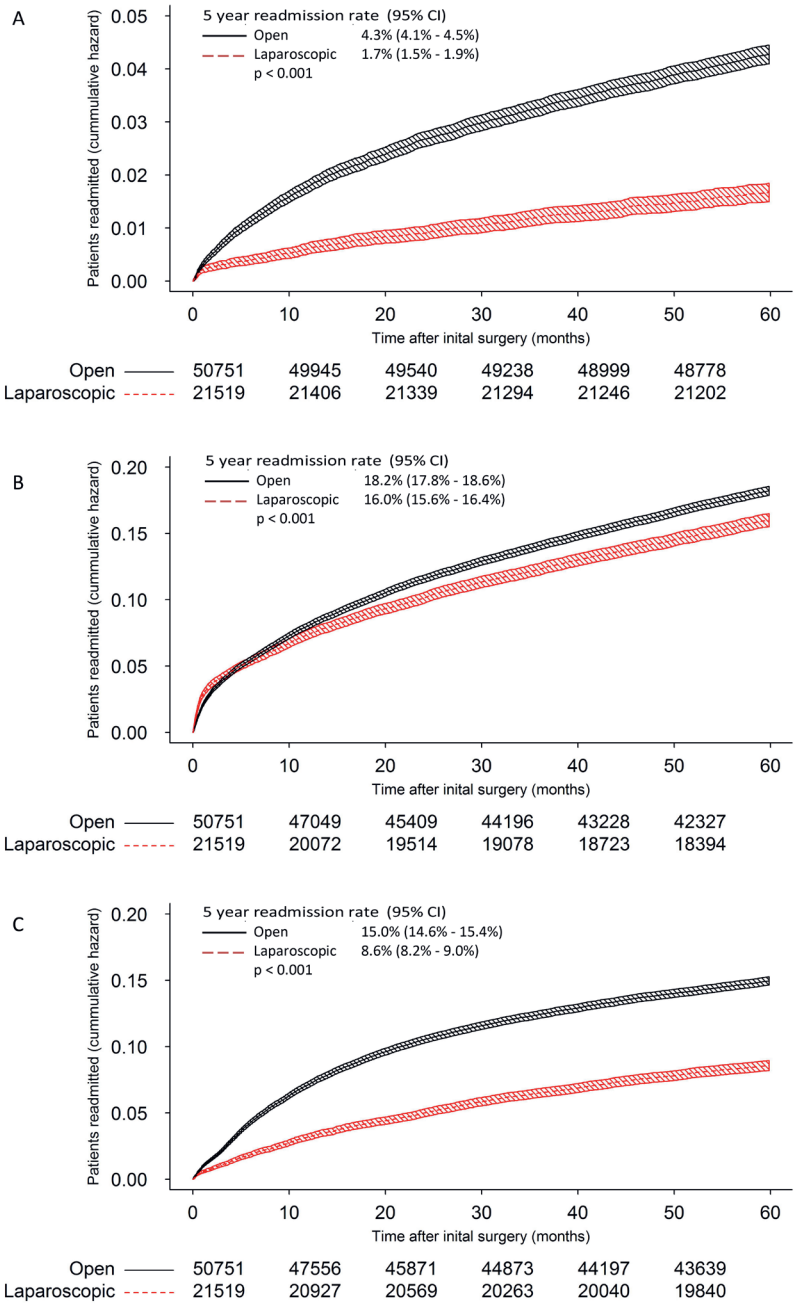



**Figure** Adhesion-related readmissions among patients who had open surgery and laparoscopic surgery. Directly-related readmissions (A), possibly-related readmissions (B) and reoperations potentially complicated by adhesions (C), among patients who had open surgery and laparoscopic surgery.

in the laparoscopic surgery cohort vs 7 592/50 751 [15·0%; 95%CI 14·6–15·4] in the open surgery cohort; figure C). In the open surgery cohort, 592 (6·2%) of 9 578 reoperations were done laparoscopically compared with 980 (43·7%) of 2 243 reoperations in the laparoscopic surgery cohort. Reoperation codes did not differ substantially between the open and laparoscopic surgery cohorts (appendix p 2).

1 548 (38·5%) of 4 021 patients who were readmitted for a disorder directly related to adhesions were readmitted within the first 2 years after index surgery. No differences were identified in the time to first readmission between the open and laparoscopic surgery cohorts (appendix pp 47, 48).

The finding that the rate of adhesion-related readmissions was lower among patients who had laparoscopic procedures than patients who had open surgeries was consistent with subgroup analyses by anatomical site of surgery, with the exception of patients who had surgery of the female reproductive tract; the proportion of readmissions directly related to adhesions did not differ significantly between the open and laparoscopic surgery cohorts at this anatomical site (4·1% vs 3·3%; table 2; appendix p 11).

Of all procedure types, patients who had surgery of the colon or rectum were the most frequently readmitted for disorders directly related to adhesions (5-year readmission rate 10·1% for colon surgery and 11·0% for rectum surgery). Patients who had a cholecystectomy or liver surgery were the least frequently readmitted for disorders directly related to adhesions (5-year readmission rate 1·3% for cholecystectomy and 2·9% for liver surgery). Patients who had laparoscopic surgery were less frequently readmitted for direct adhesion related reasons than those in the open surgery cohort across all ten categories of frequent surgical procedures, with the exception of patients who had a gynaecological procedure with hysterectomy (appendix pp 14-46).

Univariate hazard ratios for readmissions directly related to adhesions and readmissions possibly related to adhesions are shown in the appendix (pp 3, 4). In univariate analysis, surgical approach (open or laparoscopic), age, sex, malignancy as primary indication for surgery (no malignancy, malignancy of foregut, malignancy of midgut or hindgut, malignancy of female reproductive tract), and type of procedure were all found to be

**Table 2** Outcome readmissions, by operation site

| Site of index surgery | Readmissions directly related to adhesions (n=4 021) | | | Readmissions possibly related to adhesions (n=22 265) | | | Repeat surgery potentially complicated by adhesions (n=13 386) | Total readmissions |
|---|---|---|---|---|---|---|---|---|
| | Adhesiolysis procedures with or without small bowel obstruction | Adhesions with or without small bowel obstruction treated non-operatively | Gynaecological adhesions treated surgically | Abdominal surgery possibly related to adhesions | Abdominal surgery possibly related to adhesions | Abdominal surgery possibly related to adhesions | | |
| Mid or hindgut | | | | | | | | |
| Open | 1 031 (8·9 %) | 771 (6·7%) | 55 (0·5%) | 744 (6·5%) | 4 943 (42·9%) | 45 (0·4%) | 3 934 (34·1%) | 11 523 (29·0%) |
| Laparoscopic | 138 (5·6%) | 76 (3·1%) | 11 (0·4%) | 178 (7·2%) | 1 274 (51·8%) | 24 (1·0%) | 760 (30·9%) | 2 461 (6·2%) |
| Foregut or other abdominal | | | | | | | | |
| Open | 495 (4·7%) | 339 (3·3%) | 118 (1·1%) | 734 (7·0%) | 5 299 (50·5%) | 177 (1·7%) | 3 327 (31·7%) | 10 489 (26·4%) |
| Laparoscopic | 144 (2·3%) | 80 (1·3%) | 32 (0·5%) | 276 (4·5%) | 4 011 (64·8%) | 60 (1·0%) | 1 587 (25·6%) | 6 190 (15·6%) |
| Female reproductive tract | | | | | | | | |
| Open | 305 (3·7%) | 234 (2·9%) | 134 (1·6%) | 366 (4·5%) | 3 433 (41·9%) | 208 (2·5%) | 3 516 (42·9%) | 8 196 (20·7%) |
| Laparoscopic | 34 (4·2%) | 6 (0·7%) | 18 (2·2%) | 51 (6·3%) | 399 (49·1%) | 43 (5·3%) | 262 (32·2%) | 813 (2·0%) |
| Total | 2 147 (5·4%) | 1 506 (3·8%) | 368 (0·9%) | 2 349 (5·9%) | 19 359 (48·8%) | 557 (1·4%) | 13386 (33·8%) | 39 672 (100%) |

**Table 3** Multivariable analysis for direct adhesion-related readmissions

| | N/N total (%) | HR (95% CI) | P-value |
|---|---|---|---|
| Approach | | | |
| Open | 2 462/50 751 (4·9%) | Ref. | |
| Laparoscopic | 423/21 519 (2·0%) | 0·68 (0·60 - 0·77) | P < 0·001 |
| Age* (per year) | | 1·00 (1·00 -1·01) | P = 0·049 |
| Sex | | | |
| Male | 1 004/23 334 (4·3%) | Ref. | |
| Female | 1 881/48 934 (3·8%) | 1·19 (1·09 - 1·30) | P < 0·001 |
| Malignant disease | | | |
| No malignancy | 2 011/60 710 (3·3%) | Ref. | |
| Mid- or hindgut | 523/5 420 (9·6%) | 0·34 (0·28 - 0·41) | P < 0·001 |
| Foregut and other | 194/4 148(4·7%) | 0·39 (0·32 - 0·48) | P < 0·001 |
| Female reproductive tract | 157/1 992 (7·9%) | 0·44 (0·34 - 0·56) | P < 0·001 |
| Type of procedure | | | |
| Cholecystectomy | 180/14 177 (1·3%) | Ref. | |
| Liver | 12/415 (2·9%) | 1·58 (0·80 - 3·13) | P = 0·186 |
| Retroperitoneal | 83/1 827 (4·5%) | 2·67 (1·96 - 3·64) | P < 0·001 |
| Urologic | 129/3 708 (3·5%) | 2·08 (1·85 - 2·75) | P < 0·001 |
| Upper GI | 91/2 777 (3·3%) | 2·20 (1·65 - 2·94) | P < 0·001 |
| Appendectomy | 164/7 385 (2·2%) | 1·81 (1·42 - 2·30) | P < 0·001 |
| Gynaecological no uterus extirpation | 268/10 080 (2·7%) | 1·56 (1·24 - 1·96) | P < 0·001 |
| Gynaecological uterus extirpation | 222/7 641 (2·9%) | 1·22 (0·95 - 1·56) | P = 0·124 |
| Rectum | 359/3 270 (11·0%) | 6·87 (5·45 - 8·64) | P < 0·001 |
| Colon | 592/5 869 (10·1%) | 6·32 (5·08 - 7·85) | P < 0·001 |
| Other | 785/15 121 (5·2%) | 3·47 (2·83 - 4·25) | P < 0·001 |

* older patients are at higher risk

associated with risk of readmission and thus were entered into the multivariate analyses. In multivariable Cox-regression analyses, the use of a laparoscopic approach in the abdominal or pelvic cavity was a significant independent protective factor for both readmissions directly related to adhesions (hazard ratio [HR] 0·68, 95% CI 0·60–0·77) and readmissions possibly related to adhesions (HR 0·89, 0·85–0·94). In multivariable analyses, type of procedure, malignancy, sex, and age were also independent significant factors for readmissions directly or possibly related to adhesions (tables 3, 4).

**Discussion**

The rate of readmissions directly related to adhesions was approximately 30% lower among patients who had laparoscopic surgery compared with open surgery. Overall, we found that approximately one in every four patients who had surgery of the abdomen or pelvic cavity was readmitted within 5 years, for an adhesion-related cause or for a reoperation that was potentially complicated by adhesions. Half of these readmissions occurred within the first 2 years after initial surgery. The anatomical site of operation was an important predictor of directly related readmissions; patients who had surgeries of the colon or rectum were most frequently readmitted. Despite our finding that the incidence of readmissions directly related to adhesions was significantly lower among patients who had laparoscopic surgery than open surgery, this difference did not seem to translate into a subsequent decrease in overall adhesion-related readmissions at the population level compared with the original SCAR studies.[3] However, assuming that the use of laparoscopic surgery continues to increase, it is possible that a larger effect might be observed in the future.

This study assessed the effect of laparoscopic surgery on adhesion-related hospital readmissions at the population level. Previous studies have demonstrated a reduction in adhesion formation after laparoscopic surgery when compared with open surgical procedures, with the main advantage of laparoscopy being the lower incidence of adhesion formation at incision lines.[5] At present, the effect of this decrease on adhesion-related complications and overall postsurgical morbidity remains unclear because clinical trials of laparoscopy compared with open surgery have not been powered for long- term adhesion-

related outcomes.[17] By using comparable methods to the original SCAR studies, we have been able to clearly assess the extent of any progress made since the widespread adoption of laparoscopy across a range of surgical subspecialties.



A major strength of this study is the use of validated high-quality data from the Scottish Medical Record Linkage Database, managed by the NHS. Centralised reporting and low population migration enabled us to do an accurate nationwide study.[16] The study includes an unselected group of patients who had index surgeries over several years, reflecting every day surgical practice. NHS Scotland data is of high quality, and generalisable for high-income countries. This database is ideal for population-based studies due to Scotland's geographically self-contained location, low level of migration (2·4% over the years included in this study), and its derivation from a national health service with centralised reporting.

A limitation of this study is the difficulty associated with defining overall morbidity from adhesions. We considered the number of directly related readmissions as our primary outcome, although this reflects an underestimate of the true burden of adhesions. A larger number of readmissions are classified as possibly related than directly related, because symptoms of adhesion-related complications are often nonspecific and might also be caused by other conditions. Confirmation that adhesions are the true cause of symptoms often itself necessitates surgical exploration. However, most patients with adhesion-related complications are not treated operatively, and adhesiolysis is not always accurately documented in surgical reports.[18] By contrast, by primarily evaluating directly related readmissions, we can safely conclude that overestimation of the true association between adhesions and these hospital readmissions is unlikely. Compared with the original SCAR studies, we found that the proportion of readmissions classified as directly related to adhesions increased by 40% (10·1% in the present study vs 5·7% in the SCAR studies). This higher proportion of readmissions might be attributable to an increased awareness of adhesions and better coding, rather than a true increase in readmissions directly related to adhesions.[3,11]

Compared with the original SCAR studies, we observed an increase in the proportion of readmissions possibly related to adhesions, and a relatively lower number of reoperations

**Table 4** Multivariable analysis for possibly adhesion-related readmissions

| | N/N total (%) | HR (95% CI) | P-value |
|---|---|---|---|
| Approach | | | |
| Open | 10 548/50 751 (20·8%) | Ref. | |
| Laparoscopic | 3 923/21 519 (18·2%) | 0·89 (0·85 - 0·94) | P < 0·001 |
| Age* (per year) | | 1·00 (0·99 - 1·00) | P < 0·001 |
| Sex | | | |
| Male | 4 051/23 334 (17·4%) | Ref. | |
| Female | 10 420/48 934 (21·3%) | 1·42 (1·36 - 1·48) | P < 0·001 |
| Malignant disease | | | |
| No malignancy | 11 907/60 710 (19·6%) | Ref. | |
| Mid- or hindgut | 1 339/5 420 (24·7%) | 0·63 (0·57 - 0·71) | P < 0·001 |
| Foregut and other | 760/4 148 (18·3%) | 0·62 (0·54 - 0·70) | P < 0·001 |
| Female reproductive tract | 465/1 992 (23·3%) | 0·68 (0·59 - 0·78) | P < 0·001 |
| Type of procedure | | | |
| Cholecystectomy | 2 622/14 177 (18·5%) | Ref. | |
| Liver | 97/415 (23·4%) | 1·39 (1·12 - 1·72) | P = 0·003 |
| Retroperitoneal | 366/1 827 (20·0%) | 1·24 (1·10 - 1·41) | P = 0·001 |
| Urologic | 659/3 708 (17·8%) | 1·01 (0·91 - 1·12) | P = 0·836 |
| Upper GI | 552/2 777 (19·9%) | 1·09 (0·98 - 1·20) | P = 0·126 |
| Appendectomy | 1 199/7 385 (16·2%) | 0·86 (0·80 - 0·94) | P < 0·001 |
| Gynaecological no uterus extirpation | 1 829/10 080 (18·1%) | 0·77 (0·71 - 0·83) | P < 0·001 |
| Gynaecological uterus extirpation | 1 211/7 641(15·8%) | 0·61 (0·56 - 0·67) | P < 0·001 |
| Rectum | 908/3 270 (27·8%) | 1·78 (1·62 - 1·96) | P < 0·001 |
| Colon | 1 604/5 869 (27·3%) | 1·72 (1·58 - 1·87) | P < 0·001 |
| Other | 3 424/15 121 (22·6%) | 1·18 (1·10 - 1·27) | P < 0·001 |

* Older patients are at higher risk

related to adhesions. The larger proportion of possibly related readmissions observed in our study is most likely to be explained by the increase in conservative treatment of adhesive small bowel obstruction that has been adopted since the SCAR studies were published; non-operative management of adhesive small bowel obstruction accounted for 66% of all possibly related readmissions. In contrast to traditional surgical practice, recent studies[19–21] have shown that it is safe to manage most cases of adhesive small bowel obstruction non-operatively for 72 h, a finding which has been adopted by the international guidelines. At present, approximately 70% of adhesive small bowel obstruction cases are treated non-operatively.[21]

Although the relative number of laparoscopic resections greatly increased compared with the original SCAR studies, the use of laparoscopy only began to increase substantially in the past few years. For example, in an analysis of colorectal procedures in the Netherlands in 2018, 75% of procedures were laparoscopic;[22] however, follow-up is too short to assess adhesion-related readmissions. The lower rate of laparoscopies might indicate some selection bias. The net effect of this potential source of bias on the overall results are unclear. On the one hand, surgeons captured in the study might still have been in the earlier stages of their respective laparoscopic learning curves. Adhesion-related morbidity in laparoscopy might be higher for surgeons with less laparoscopic experience. On the other hand, laparoscopic surgery is typically used for routine cases initially, and open surgery is increasingly reserved for more extensive surgical procedures and cases that are anticipated to be difficult.[23] Some of the severe adhesion formation often observed following difficult surgeries might have been induced by the disease process and peritoneal inflammation rather than from the surgical approach used. The effect of laparoscopic surgery also seemed to decrease after correcting for case-mix variables, such as type of procedure in multivariate analysis. More in-depth surgical and patient-related case-mix variables (such as surgical duration, surgeon experience, exact reason for surgical conversion to open surgery, body-mass index, American Society of Anesthesiologists class, and socio- economic status of patients) were not available for analysis in the population database, and thus could not be included our models.

On a population level, 35% of patients were readmitted in the original SCAR studies during the 10-year follow- up period compared with 27% in the present study during the 5-year follow-up period. Considering that approximately 70% of all adhesion-related complications occur in the first 5 years after index surgery,[2,3] the readmission rates are roughly comparable. Although at present the use of laparoscopic techniques continues to increase, future population effects on adhesion-related morbidity might be more substantial. Improved registration and awareness of adhesion-related complications might have also contributed to the fact that readmission rates remained comparable. This population-based analysis with long-term follow-up remains one of the most robust assessments to date of the long-term impact of the introduction of laparoscopy on overall morbidity of adhesions and resulting health-care utilisation.

Our study demonstrates that even after the widespread adoption of laparoscopic surgery, morbidity related to adhesions remains substantial. As many as one in six patients treated laparoscopically were readmitted for a possible adhesion related complication, 1·7% of whom were readmitted for a direct adhesion related complication. Most admissions for adhesions were for adhesive small bowel obstruction. Health-care costs for adhesion-related complications are also substantial. For example, treatment costs for adhesive small bowel obstruction are estimated at €16 305 for operative treatment and €2 277 for non-operative treatment.[24] Furthermore, the true burden of adhesions is even higher, since these figures do not account for the morbidity of chronic pain that often results in outpatient visits.[25] Additionally, chronic abdominal pain after surgery rarely results in readmission. Chronic pain related to adhesions has a considerable societal impact, including opioid use, reduced quality of life, and employment disruptions.[26,27] Although accurate assessment of the burden of chronic pain related to adhesions is difficult, promising diagnostic developments such as cine-MRI hold promise for the differentiation of chronic pain from adhesions and other causes, thereby improving personalised treatment of adhesions and research in this field.[26]

The impact of adhesions after laparoscopic surgery seems to be frequently underestimated; only 35% of surgeons routinely inform patients of the risk of adhesions before a laparoscopic procedure.[11] Morbidity after specific laparoscopic procedures, such as

colorectal operations, might further be reduced with the use of adhesion barriers.[1,13] Many of the barriers currently available are not suitable for laparoscopic surgery because they are difficult to place laparoscopically or because few safety assessments have been done in the context of bowel anastomoses. More research is therefore needed to develop measures that can be easily applied have relatively low costs.

Laparoscopic surgery reduces the incidence of adhesion-related readmissions. However, despite this effect, the overall burden of adhesion-related readmissions remains high at the population level. The continued increase in laparoscopic procedures is expected to further reduce adhesion-related morbidity at the population level. Future research is needed with regard to techniques and technologies to further reduce the incidence of adhesions and adhesion-related complications.

## References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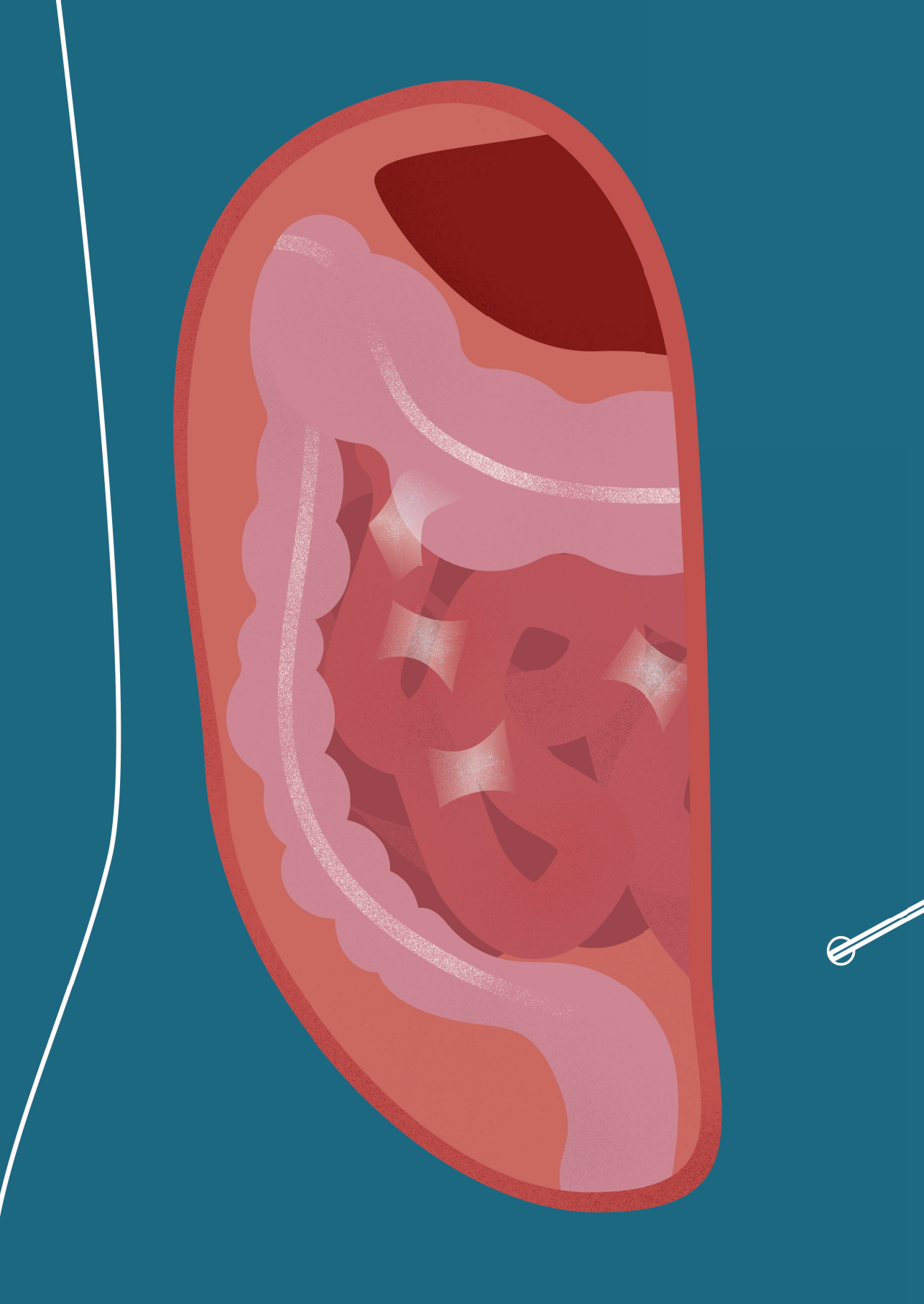
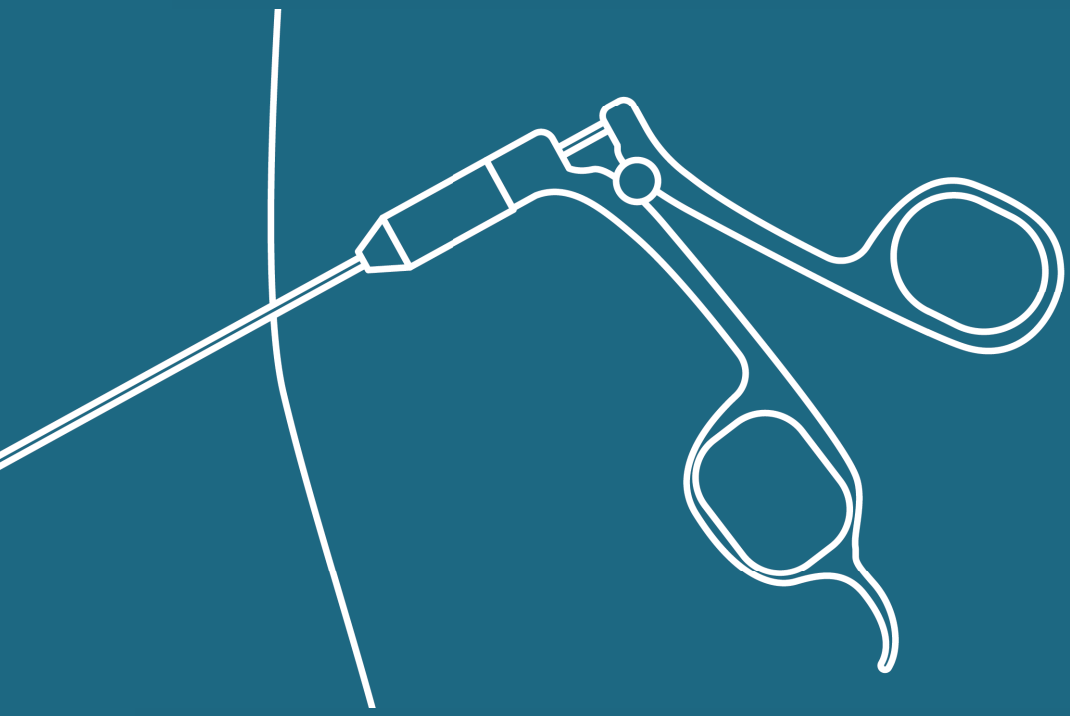


# 3

# Adhesion-related readmissions after open and laparoscopic colorectal surgery in 16 524 patients (SCAR update colorectal)



Pepijn Krielen, Richard P.G. ten Broek, Koen van Dongen, Mike C. Parker, Ewen A. Griffiths, Harry van Goor, Martijn W.J. Stommel

Submitted

**Abstract**

*Background*

Colorectal surgery is associated with a high risk of adhesion formation and subsequent complications. Recent evidence shows that laparoscopic surgery reduces adhesion formation by 50% in colorectal surgery but the effect on adhesion-related complications remains unknown. The aim of this study was to assess the effect of the implementation of laparoscopic colorectal surgery on the incidence of adhesion-related readmissions.

*Methods*

Population data from the Scottish National Health Service were used to identify patients who underwent colorectal surgery between June 2009 and June 2011. Readmissions were registered and screened until December 2017 and categorized as being either directly or possibly related to adhesions, or as reoperations potentially complicated by adhesions. The primary outcome measure was the difference in incidence of directly adhesion-related readmissions between the open and laparoscopic cohort.

*Findings*

Colorectal surgery was performed in 16 524 patients; 4 455 (27%) underwent laparoscopic surgery. Readmission rates for any adhesion-related cause were 4 658/12 069 (39%) in the open and 1 179/4 455 (26%) in the laparoscopic cohort. Patients undergoing laparoscopic surgery were readmitted less frequently for directly adhesion-related complications, 2.4% (95% CI 2.0 - 2.8%) vs. 7.5% (95% CI 7.1 - 7.9%) in the open cohort. Readmissions for possibly adhesion-related complications were less frequent in the laparoscopic cohort, 16.8% (95% CI 15.6 - 18.0%) vs. 21.7% (95% CI 20.9 - 22.5%), as well as reoperations potentially complicated by adhesions, 9.7% (95% CI 8.9 - 10.5%) vs. 16.9% (95% CI 16.3 - 17.5%).

*Interpretation*

Overall any adhesion-related readmissions occurred in one in three patients after open colorectal surgery and one in four in laparoscopic surgery. Incidence rates of adhesion-related complications remain substantial even after laparoscopic surgery.

**Introduction**

After colorectal surgery the vast majority of patients develop intra-abdominal or pelvic adhesions.[1,2] The clinical impact of adhesion formation varies, but can be substantial, including a lifelong risk of readmissions for adhesive small bowel obstruction (ASBO), chronic pain or infertility.[2-4] Moreover adhesions can necessitate adhesiolysis during reoperations increasing the risk of inadvertent bowel injury.[5] In over one in four operative procedures complicated by adhesions, inadvertent bowel injury occurs, with a subsequent increased incidence of post-operative complications.[5,6]

Two decades ago the population based Surgical and Clinical Adhesions Research (SCAR) studies were the first to determine the extent to which adhesion formation contributes to hospital readmissions.[7,8] These landmark studies revealed that over one in three patients were readmitted for adhesion-related causes in the ten years after colorectal surgery.[2] The first and most important effect of the publication of these studies was the emergence of awareness of adhesion-related complications. The study group stated in 2001 that in order to reduce the substantial clinical impact of adhesion formation, implementation of adhesion prevention strategies should be given a high priority.[8]

In addition to the use of adhesion prevention agents, minimizing the peritoneal damage of surgery by means of a laparoscopic approach was considered the most viable strategy. A common assumption of many surgeons is that the problem of postoperative adhesion formation is fairly minimal due to the wide implementation of laparoscopic surgery over the past decades.[9] Studies report reduced incidence rates of adhesion formation after laparoscopic colorectal cancer surgery compared with open surgery.[1,10] However, three in five patients still develop adhesions after laparoscopic colorectal procedures.[1] Moreover, the reduction in adhesion formation might not correlate with a proportional reduction in long-term adhesion-related complications. A single adhesive band can cause a severe case of ASBO, while extensive dense adhesions can be asymptomatic.[11] Studies on the incidence of ASBO after laparoscopic surgery do not consistently show a risk reduction.[12-16] Some retrospective cohort studies report a reduced risk of ASBO after laparoscopic colorectal surgery[16], however trials report no difference in incidence rates.[12,13] The recently published

SCAR update study, a nationwide retrospective cohort study, revealed an undiminished high incidence of adhesion-related readmissions (including ASBO) after abdominal surgery in the minimally invasive era.[17]

Results from this study are of the utmost importance for colorectal surgeons, since colorectal surgery is known for its adhesion formation propensity and the vast majority of contemporary colorectal procedures are performed laparoscopically. [1,2] Laparoscopic surgery reduces adhesion formation, however the effects on clinically relevant parameters (e.g. readmissions) is lacking. The current population based study aims to compare the incidence of adhesion-related readmissions after laparoscopic and open colorectal surgery.

**Methods**

In this study population data were used from the Scottish Medical Record Linkage Database, managed by the Scottish National Health Service (NHS Scotland) Information and Statistics Division. All Scottish individual patients' records on inpatient hospital admissions and day care hospital admissions were included. Data from the NHS were validated at hospital level by an annual audit.[18,19] The database was previously described in detail by the SCAR research group.[7,8]

All patients undergoing open or laparoscopic colorectal surgery between June 2009 and June 2011 were included. Patients with a history of abdominal or pelvic surgery were excluded. Colorectal surgery was defined by the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) codes for surgery on the colon (H01 - H19) or the rectum (H33 - H 36, H 41). Based on the OPCS-4 coding, patients were categorized as open or laparoscopic approach to the abdominal cavity. Procedures were classified in such a way that each individual patient would only fit in one of the predefined categories.

Readmissions were screened and registered until December 2017 based on relevant predefined International Classification of Diseases, tenth edition (ICD-10) and OPCS-4 codes. According to previous SCAR methodology[7,8], readmissions were categorized as being

1) directly related to adhesions (e.g. adhesive small bowel obstruction, adhesiolysis), 2) possibly related to adhesions (e.g. small bowel obstruction) or 3) reoperations potentially complicated by adhesions (e.g. left colectomy after sigmoid resection). Readmissions which were considered to be unrelated to adhesions fell outside the scope of this study. Directly adhesion-related readmissions were only scored if there was an explicit reference to adhesions in the OPCS-4 or ICD-10 code. The most common ICD-10 codes for possibly adhesion-related readmissions are reported in a previous publication, mainly consisting of different codes for abdominal pain or absence of stool.[17]



The primary outcome measure was the incidence of directly adhesion-related readmissions at 5 years following index surgery, in the open and laparoscopic colorectal surgery cohort. Secondary outcome measures were the incidence of possibly adhesion-related readmissions and reoperations potentially complicated by adhesions. In the analysis of readmissions possibly related to adhesions, the incidence of first directly or possibly adhesion-related readmissions was recorded.

Malignancy is the usual indication for rectal surgery; for colonic surgery a malignancy is not always the indication for surgery. Colonic surgery could be instigated for benign reasons like diverticulosis or inflammatory bowel diseases. Results from our analysis could be biased by the indication for surgery. For these reasons primary and secondary outcomes were analyzed separately for the overall cohort and for procedures on the colon or rectum. Subgroup analyses were performed for frequent surgical procedures: appendectomy, left hemicolectomy, right hemicolectomy, (sub)total colectomy, sigmoidectomy, rectal excision (including low anterior resection), rectal prolapse, colostomy or other colorectal procedures.

The incidence of adhesion-related readmissions was demonstrated by Kaplan-Meier plots. Log-rank tests were used to determine significant differences in survival between groups. Multivariate Cox regression analysis was performed to determine if a laparoscopic or open approach to the abdominal cavity was an independent and significant risk factor for adhesion-related readmissions. All variables associated with adhesion-related readmissions in univariate analysis ($p<0.2$) or based on clinical relevance were taken into account in

multivariate analysis. Backward stepwise selection was performed. Statistical analysis was performed using SPSS software (version 22.0) and R 3.5.1. Significant differences were defined as $p<0.05$.

*Role of the funding source*

This study received no funding for the design, data collection, analysis, interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

A total of 16 524 patients underwent colorectal surgery. Surgery on the colon was performed in 13 254 patients of whom 30.9% underwent laparoscopic surgery. Surgery on the rectum was performed in 3 270 of whom laparoscopic surgery was performed in 10.9%. Demographics of the study population are reported in *table 1.* The mean follow up for all cohorts was 67 months. In the 5 years following index surgery 5 837 (35.3%) patients were readmitted at least once for an adhesion-related cause. In the laparoscopic cohort patients were readmitted less frequently for an adhesion-related cause compared with the open cohort, 26.5% vs. 38.6% respectively, $p < 0.005$ (*figure 1)*.

*Directly adhesion-related*

In the overall cohort 1 008 (6.1%) patients were readmitted at least once for a complication directly related to adhesions, (*table 2)*. In the laparoscopic cohort less patients were readmitted for a complication directly related to adhesions compared with the open cohort, 107/4 455 (2.4%) vs. 901/12 069 (7.5%), $p < 0.005$ (*figure 2)*. Sub-analyses of the colon and rectum group showed similar trends. In the colon group 596/9 156 (6.5%) of all patients with open surgery were readmitted compared with 82/4 098 (2.0%) in the laparoscopic cohort, $p < 0.005$ (*figure 3)*. In the rectum group 305/2 913 (10.5%) and 25/357 (7.0%) respectively, $p = 0.044$ (*figure 4)*.

**Table 1** Demographics of study population

| | Colon | | Rectum | | Total | |
|---|---|---|---|---|---|---|
| | Open | Laparoscopy | Open | Laparoscopy | Open | Laparoscopy |
| | N = 9 156 | N = 4 098 | N = 2 913 | N = 357 | N = 12 069 | N = 4 455 |
| Sex | | | | | | |
| Male | 4 936 (53.9%) | 2 038 (49.7%) | 1 408 (48.3%) | 172 (48.2%) | 6 344 (52.6%) | 2 210 (49.6%) |
| Female | 4 219 (46.1%) | 2 060 (50.3%) | 1 505 (51.7%) | 185 (51.8%) | 5 724 (47.4%) | 2 245 (50.4%) |
| Age | | | | | | |
| Min | 0 | 0 | 0 | 16 | 0 | 0 |
| Max | 101 | 95 | 96 | 91 | 101 | 95 |
| Mean | 49 | 34.7 | 66 | 65 | 54 | 37 |
| Follow-up (months) | | | | | | |
| Min | 0 | 0.2 | 0.1 | 0.8 | 0 | 0.2 |
| Max | 95.2 | 91.2 | 91.3 | 90.9 | 95.2 | 91.2 |
| Mean | 65.1 | 73.3 | 61.7 | 66.6 | 64.2 | 72.7 |
| Surgical procedure | | | | | | |
| Appendectomy | 4 115 | 3 270 | - | - | 4 115 | 3 270 |
| Left hemicolectomy | 340 | 55 | - | - | 340 | 55 |
| Right hemicolectomy | 2 312 | 396 | - | - | 2 312 | 396 |
| (Sub)Total colectomy | 728 | 74 | - | - | 728 | 74 |
| Sigmoidectomy | 756 | 155 | - | - | 756 | 155 |
| Colostomy | 506 | 128 | - | - | 506 | 128 |
| Rectum prolaps | - | - | 272 | 58 | 272 | 58 |
| Rectum excision | - | - | 2 568 | 296 | 2 568 | 296 |
| Other | 399 | 20 | 73 | 3 | 472 | 23 |

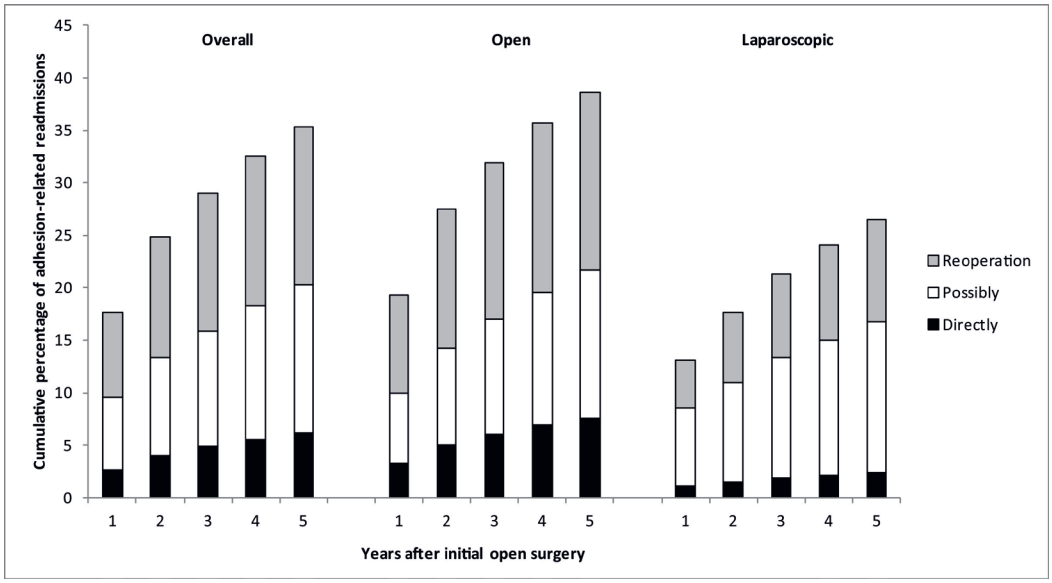



**Figure 1** Cumulative percentage of adhesion-related readmissions. Patients with multiple readmissions were counted only once. If a patient had both a directly and possibly adhesion-related readmission, the patient was included in the bar for directly adhesion-related readmissions.

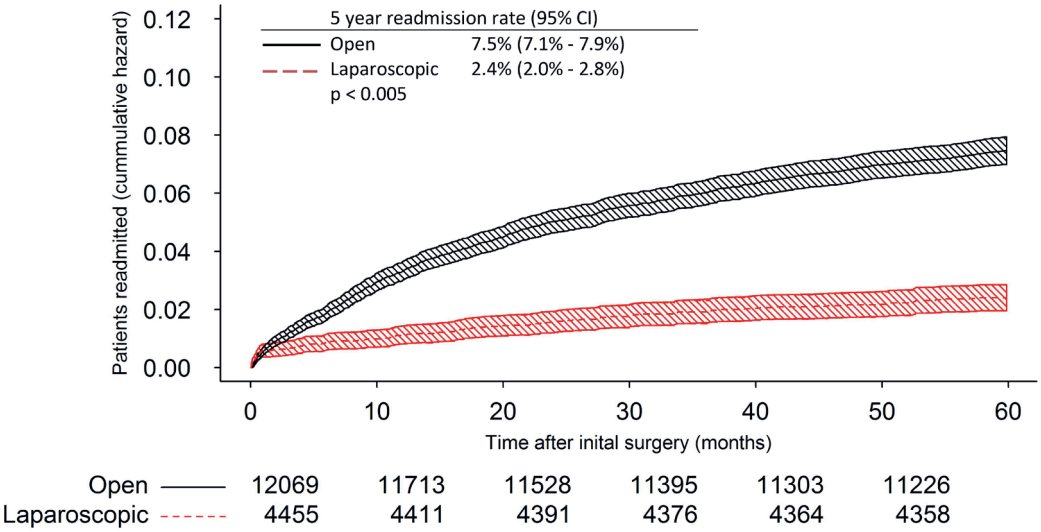



**Figure 2** Cumulative directly adhesion-related readmission rates for the overall cohort

**Table 2** Readmission rates for patients with surgery on the colon or rectum

| | Colon | | | Rectum | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | Open N = 9 156 | Laparoscopy N = 4 098 | P-value | Open N = 2 913 | Laparoscopy N = 357 | P-value | Open N= 12 069 | Laparoscopy N = 4 455 | P-value |
| Directly | 596 (6.5%) | 82 (2.0%) | p < 0.005 | 305 (10.5%) | 25 (7.0%) | p = 0.044 | 901 (7.5%) | 107 (2.4%) | p < 0.005 |
| Possibly | 1 859 (20.3%) | 671 (16.4%) | p < 0.005 | 754 (25.9%) | 78 (21.8%) | p = 0.088 | 2 613 (21.7%) | 749 (16.8%) | p < 0.005 |
| Reoperation | 1 161 (12.7%) | 328 (8.0%) | p < 0.005 | 884 (30.3%) | 102 (28.6%) | p = 0.534 | 2 045 (16.9%) | 430 (9.7%) | p < 0.005 |

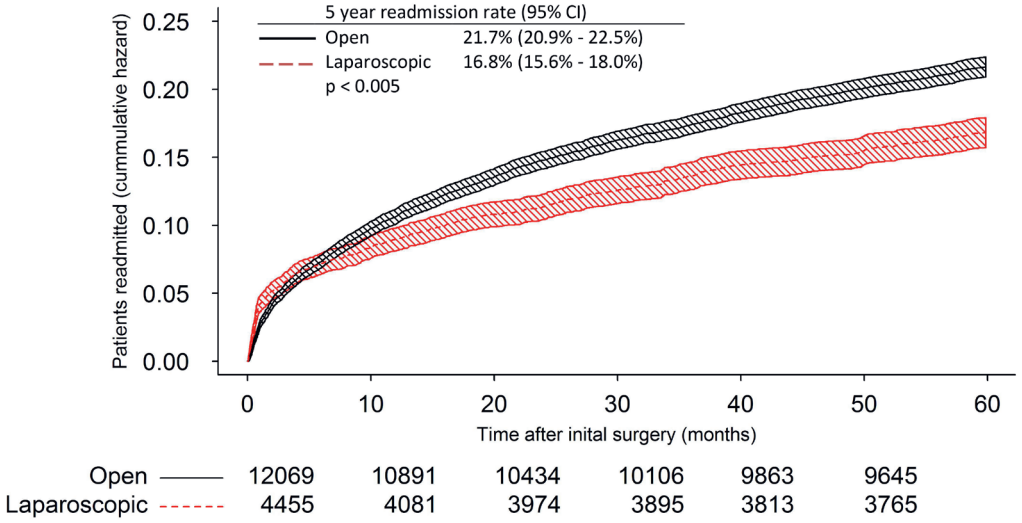



**Figure 3** Cumulative directly adhesion-related readmission rates for patients operated on the colon

*Possibly adhesion-related*

A total of 3 362 (20.3%) patients were readmitted for possibly adhesion-related complications. Possibly adhesion-related readmissions in the laparoscopic cohort were less frequent compared with the open cohort, 749/4 455 (16.8%) vs. 2 613/12 069 (21.7%), p < 0.005. Laparoscopic surgery on the colon was associated with lower rates of readmissions compared with open surgery, 671/4 098 (16.4%) vs. 1 859/9 156 (20.3%), p < 0.005. Possibly adhesion-related readmissions did not differ between the open and laparoscopic cohort in surgery on the rectum, (*table 2)*.

*Reoperations potentially complicated by adhesions*

A total of 2 475 (15.0%) patients were readmitted for a reoperation potentially complicated by adhesions in the five years following initial surgery. Of these, 9.6% of reoperations were performed laparoscopically. Less patients in the laparoscopic cohort underwent reoperations compared with the open cohort, 430/4 455 (9.7%) vs. 2 045/12 069 (16.9%), p < 0.005. A laparoscopic approach for reoperation was more commonly performed if the

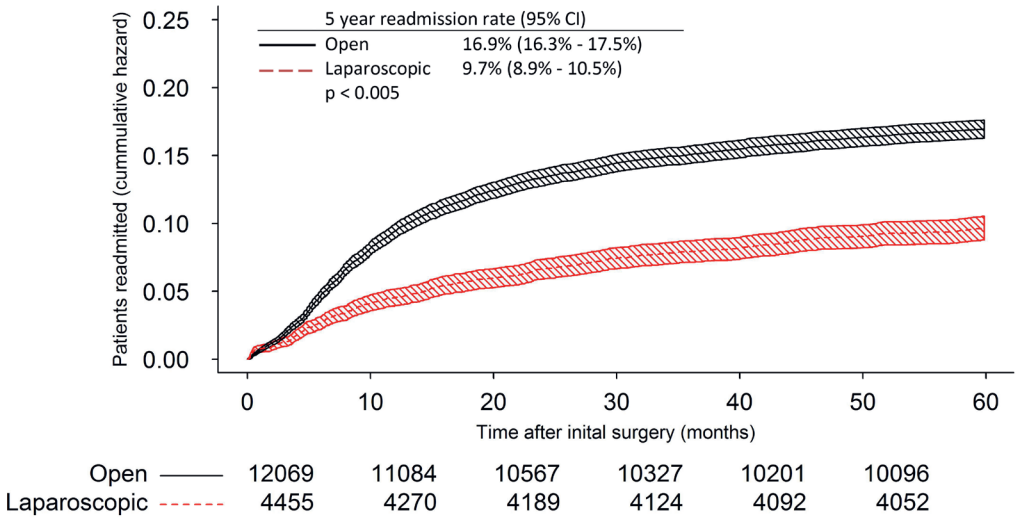



**Figure 4** Cumulative directly adhesion-related readmission rates for patients operated on the rectum

index surgery was laparoscopic compared with open index surgery, 86/430 (20.0%) vs. 151/2 045 (7.4%), p < 0.005. Reoperations in patients with surgery on the colon were less common in the laparoscopic cohort compared with the open cohort, 328/4 098 (8.0%) vs. 1 161/9 156 (12.7%). Incidence rates of reoperations did not differ between laparoscopic and open surgery in patients who underwent surgery on the rectum, (*table 2)*.

*Time to first adhesion-related readmission*

In the first year following index surgery 2.3% of all patients in the overall cohort were readmitted for a complication directly related to adhesions, increasing to 4.4% after 5 years. In the open cohort 2.9% of patients were readmitted for directly adhesion-related complications in the first year which increased to 5.4% after 5 years. In the laparoscopic cohort 1.0% of patients were readmitted for directly adhesion-related complications in the first year after index surgery rising to 1.6% after 5 years. Readmission rates for possibly adhesion-related complications and reoperations potentially complicated by adhesions are presented in *figure 1.*

*Type of surgical procedure*

Five year adhesion-related readmission rates for all common types of colorectal procedures are presented in *table 3* and survival curves are presented in *appendix figure 1a-12c.* Patients who underwent a laparoscopic appendectomy, right hemicolectomy or sigmoidectomy were readmitted less frequently for directly adhesion-related complications compared with open procedures. There were no differences in directly adhesion-related readmissions between the open and laparoscopic cohort for left hemicolectomies, (sub)total colectomies, procedures for a rectal prolapse, rectal excisions, colostomy procedures or other colorectal procedures. Readmissions for directly adhesion-related complications were the least frequent for patients who underwent an appendectomy, 151/7 385 (2.0%). Patients who underwent a (sub)total colectomy were readmitted the most for directly adhesion-related complications, 121/802 (15.1%).

*Uni- and multivariate analysis*

In univariate analysis laparoscopic surgery was associated with a decrease in directly adhesion-related readmissions, HR 0.31 (95% CI 0.26 - 0.38). Parameters associated with an increased risk of directly adhesion-related readmissions were type of surgical procedure, malignancy as the indication for surgery, female sex and increasing age, (*appendix table 1)*. In multivariate analysis laparoscopic surgery was associated with a decrease in directly adhesion-related readmissions, HR 0.52 (95% CI 0.42 - 0.64). In multivariate analyses parameters that significantly and independently increased the risk of directly adhesion-related readmissions were type of surgical procedure and female sex, (*table 4).*

**Discussion**

The implementation of laparoscopic surgery for colorectal procedures has resulted in a decrease of adhesion-related readmissions. Of 16 524 patients who underwent colorectal surgery between June 2009 and June 2011, over one in three patients were readmitted in

**Table 3** Directly adhesion-related readmission rates per common colorectal procedure

| Index surgery | Total number of patients (%) | Total number of patients readmitted (%) | Total number of directly adhesion-related readmissions | Average per patient |
|---|---|---|---|---|
| **Appendectomy** | | | | |
| Open | 4 115 (55.7%) | 111 (2.7%) | 144 | 1.3 |
| Laparoscopic | 3 270 (44.3%) | 40 (1.2%) | 51 | 1.3 |
| **Left hemicolectomy** | | | | |
| Open | 340 (86.1%) | 25 (7.4%) | 35 | 1.4 |
| Laparoscopic | 55 (13.9%) | 2 (3.6%) | 2 | 1.0 |
| **Right hemicolectomy** | | | | |
| Open | 2 312 (85.4%) | 188 (8.1%) | 247 | 1.3 |
| Laparoscopic | 396 (14.6%) | 14 (3.5%) | 20 | 1.4 |
| **(Sub)Total colectomy** | | | | |
| Open | 728 (90.8%) | 110 (15.1%) | 174 | 1.6 |
| Laparoscopic | 74 (9.2%) | 11 (14.9%) | 18 | 1.6 |
| **Sigmoidectomy** | | | | |
| Open | 755 (83.0%) | 76 (10.1%) | 112 | 1.5 |
| Laparoscopic | 155 (17.0%) | 5 (3.2%) | 6 | 1.2 |
| **Rectal prolapse** | | | | |
| Open | 272 (82.4%) | 7 (2.6%) | 9 | 1.3 |
| Laparoscopic | 58 (17.6%) | 2 (3.4%) | 2 | 1.0 |
| **Rectal excision** | | | | |
| Open | 2 568 (89.7%) | 292 (11.4%) | 415 | 1.4 |
| Laparoscopic | 296 (10.3%) | 23 (7.8%) | 31 | 1.4 |
| **Colostomy** | | | | |
| Open | 506 (79.8%) | 60 (11.9%) | 74 | 1.2 |
| Laparoscopic | 128 (20.2%) | 9 (7.0%) | 17 | 1.9 |
| **Other** | | | | |
| Open | 472 (95.4%) | 32 (6.8%) | 46 | 1.4 |
| Laparoscopic | 23 (4.6%) | 1 (4.3%) | 1 | 1.0 |
| **Overall** | | | | |
| Open | 12 069 (73.0%) | 901 (7.5%) | 1 256 | 1.4 |
| Laparoscopic | 4 455 (27.0%) | 107 (2.4%) | 148 | 1.4 |

the five years following surgery for any adhesion-related complication. Readmission rates for any adhesion-related complication were one in four patients in laparoscopic surgery and one in three patients in open surgery. Directly adhesion-related readmissions were reduced threefold in laparoscopic surgery compared with open colorectal surgery. Possibly adhesion-related readmissions and reoperation rates were lower in laparoscopic surgery but the decrease was less striking. Despite the decrease in adhesion-related readmissions after laparoscopic surgery, the burden of adhesions in colorectal surgery remains substantial.

A major strength of this study is the specifically chosen colorectal population, for which the potential reduction of adhesion-related complications by implementation of laparoscopy could be most important. Colorectal surgery is frequently performed for multiple common diagnoses and is notorious for the greatest risk of inducing adhesion-related complications.[7,17] The promise that laparoscopy holds for this population is amplified by the fact that at present laparoscopy has become the preferred approach for many colorectal procedures.[20,21] Previous studies reported a lower incidence of adhesions after laparoscopic colorectal surgery.[1,10] However, the effect of the broad implementation of a laparoscopic approach in colorectal surgery on clinically relevant parameters remains unknown. This study is the first to provide insight into differences between open and laparoscopic surgery on clinically and patient relevant outcome parameters.

Another strength is the use of a population database that reports the impact on adhesion-related readmissions of the implementation of laparoscopy in colorectal surgery. Data from the NHS lend themselves perfectly for population based studies due to Scotland's' geographically self-contained location with centralized reporting. Data from the NHS are validated annually by an audit of 1% of local hospital data compared with centrally held data.[22]

To assess the true effect of adhesions on hospital readmissions all readmissions were classified by their degree of certainty of adhesion relation. Only readmissions with an

**Table 4** Multivariate analysis for directly adhesion-related readmissions

| | N/N total (%) | HR (95% CI) | P-value |
|---|---|---|---|
| Approach | | | |
| Open | 901/12 069 (7.5%) | Ref. | |
| Laparoscopic | 107/4 455 (2.4%) | 0.52 (0.42 - 0.64) | p < 0.005 |
| Age | | 0.99 (0.99 - 1.00) | p = 0.084 |
| Sex | | | |
| Male | 474/8 554 (5.5%) | Ref. | |
| Female | 534/7 969 (6.7%) | 1.23 (1.08 - 1.39) | p < 0.005 |
| Indication surgery | | | |
| No malignancy | 508/11 088 (4.6%) | Ref. | |
| Malignancy colon | 284/3 457 (8.2%) | 1.12 (0.93 - 1.36) | p = 0.236 |
| Malignancy rectum | 216/1 979 (10.9%) | 1.08 (0.85 - 1.37) | p = 0.549 |
| Type of colorectal procedure | | | |
| Appendectomy | 151/7 385 (2.0%) | Ref. | |
| Left hemicolectomy | 27/395 (6.8%) | 2.96 (1.90 - 4.61) | p < 0.005 |
| Right hemicolectomy | 202/2 702 (7.5%) | 3.24 (2.49 - 4.21) | p < 0.005 |
| (sub)total colectomy | 121/802 (15.15%) | 6.69 (5.17 - 8.65) | p < 0.005 |
| Sigmoidectomy | 81/911 (8.9%) | 4.06 (3.00 - 5.49) | p < 0.005 |
| Rectal prolapse | 9/330 (2.7%) | 1.17 (0.59 - 2.33) | p = 0.653 |
| Rectal excision | 315/2 864 (11.0%) | 4.97 (3.73 - 6.63) | p < 0.005 |
| Colostomy | 69/634 (10.9%) | 5.00 (3.67 - 6.82) | p < 0.005 |
| Other | 33/495 (6.7%) | 2.80 (1.89 - 4.16) | p < 0.005 |

explicit reference to adhesions were classified as being directly related to adhesions. Unfortunately, adhesions can only be confirmed during reoperation. An explicit reference to adhesions for patients who are not operated during their readmission is therefore rare. Using this strict definition, only the verifiable effect of adhesions was studied, probably underestimating the total effect of adhesions on hospital readmissions.

The proportion of patients in this study that underwent a laparoscopic procedure seems relatively low. In our study one in three patients underwent laparoscopic surgery between June 2009 and June 2011, while in the Netherlands in 2018 over 75% of all colorectal resections were performed using a laparoscopic approach.[20] The relatively low rate of laparoscopic procedures might indicate that laparoscopic surgery was only utilized for selected cases and that surgeons are still in their laparoscopic learning curves. Moreover, due to the retrospective design of this study with five year follow-up, current practice has evolved with changes in laparoscopic techniques (e.g. extracorporeal versus intracorporeal anastomosis[23], trans anal total mesorectal excison (TA-TME)[24,25]) potentially resulting in less peritoneal wound surface, decreased adhesion formation and subsequent complications. Over the past few decades laparoscopy became the standard approach for routine procedures and also increasingly for more difficult procedures. When correcting for the type of colorectal procedure performed, laparoscopic surgery was associated with less directly adhesion-related readmissions compared with open surgery in appendectomies, right hemicolectomies and sigmoidectomies. When reviewing the Kaplan-Meier curves critically for directly adhesion-related readmissions of all other colorectal procedures, readmission rates seem to differ visually but differences between groups were not statistically significant. Differences between groups may not be statistically significant due to the relatively low number of patients in these groups. In patients with a (sub)total colectomy, directly adhesion-related readmission rates do not seem to differ between groups, (14.9% in laparoscopic and 15.1% in open procedures). (Sub)total colectomies are associated with a large peritoneal wound surface regardless of the surgical approach. The reduction in peritoneal wound surface in laparoscopic procedures compared with open is relatively small. Therefore, adhesion formation might not be significantly impacted by a laparoscopic approach in this procedure. With the increase of laparoscopic procedures and the improvement of laparoscopic techniques, the overall impact of laparoscopic surgery on adhesion-related readmissions on population level is likely to increase.

Peritoneal wound surface is not the only parameter that predicts adhesion formation. Other factors that predict adhesion formation are intra-operative blood loss, indication for surgery, type of procedure, duration of surgery and post-operative intra-abdominal

infections.[2,26,27] Laparoscopic surgery reduces peritoneal wound surface as well as intra-operative blood loss but, often prolongs operative time. Type of procedure and incidence of post-operative intra-abdominal infections are not affected by a laparoscopic or open approach. We were not able to correct for intra-operative blood loss, operative time and incidence of post-operative complications, since these data were not included in the NHS database. To the authors' knowledge no other nationwide database holds more detailed information on adhesion-related readmissions.



In multivariate analysis laparoscopic surgery was associated with a lower rate of directly adhesion-related readmissions (HR 0.52). More extended surgical procedures and female sex were associated with an increase in directly adhesion-related readmissions (*table 4*). The increase in adhesion-related readmissions in women is explained by fertility problems caused by adhesions. Adhesions are a major contributor to sub- or infertility in woman, reoperations for these indications increase the rate of readmissions for adhesion-related causes.[3]

A potential limitation that needs to be discussed is the lack of data on emergency procedures compared with elective procedures. Emergency surgical procedures are often complicated by severe infections or perforations of the bowel due to disease itself of peritoneal inflammation. For these reasons emergency abdominal procedures are more prone to adhesion formation. Unfortunately, data on emergency procedures were not available for analysis and therefore could not be included.

The colorectal SCAR study by Parker et al. in 2004, reported a four year readmission rate for directly adhesion-related readmissions after open colorectal surgery of 4.8%.[2] In the present study 7.5% of all patients after open colorectal surgery were readmitted for directly adhesion-related complications in the 5 years following surgery, so readmission rates for patients who underwent open colorectal surgery did not decrease in the past few decades and might even have increased. An increase in adhesion-related readmissions after open colorectal surgery can possibly be explained by selection of less complex cases for laparoscopic surgery and more complex cases for an open approach. For more difficult cases

and extensive surgical procedures, open surgery is still considered more appropriate. Part of the adhesion formation might therefore be explained by the peritoneal inflammatory response induced by the extensive surgical procedure or disease itself, rather than from the surgical approach. This hypothesis is supported by our data on extensive surgical procedures (i.e. (sub)total colectomy); no difference was observed in directly adhesion-related readmissions between the open and laparoscopic cohort.

In a study on adhesion formation after colorectal surgery confirmed by second-look surgery, laparoscopy reduced adhesion formation primarily to the ventral wall.[1] However, three in five patients still developed adhesions after laparoscopic surgery. A reduction in the extent of adhesion formation is not guaranteed to reduce adhesion-related complications.[11] However, a decrease in adhesion formation and severity will likely decrease the need for (extensive) adhesiolysis during reoperations and therefore reduce adhesiolysis-related complications, e.g. enterotomies. Some studies reported lower incidence rates of ASBO after laparoscopic surgery. However comparative trials report no difference in incidence rates.[12-16] In the present study laparoscopic surgery was associated with decreased incidence rates of directly adhesion-related readmissions compared with open surgery, 2.4% vs. 7.5% respectively. Moreover, in the laparoscopic cohort less patients were readmitted for reoperations potentially complicated by adhesions compared with the open cohort, 10% vs. 17%. Data from the present study support the hypothesis that laparoscopic surgery reduces adhesion-related post-operative morbidity. However, a substantial proportion of patients who underwent laparoscopic colorectal procedures were still readmitted for adhesion-related complications.

This study provides solid evidence that, contradictory to common opinions[9], laparoscopic surgery does not ensure complete banishment of adhesion-related complications. Still over one in twenty patients were readmitted for directly adhesion-related complications, one in six for possibly and one in seven for a reoperation potentially complicated by adhesions in the five years following index laparoscopic colorectal surgery. Given the high impact of adhesion-related readmissions on a population level, better techniques are necessary to reduce post-operative adhesion formation and its subsequent complications. Adhesion

barriers have proven to be safe to use, reduce adhesion formation and are cost-effective in routine use after open surgery.[28,29] Despite these results adhesion barriers are still seldom applied.[30] Most of the currently available adhesion barriers are developed and studied for open surgery. Future research should focus on barriers that are easy to apply in laparoscopic surgery (e.g. sprays, gels) and can be manufactured on a large scale at relatively low costs. Most of the current trials only report adhesion-related complications as a secondary endpoint with a short term follow-up, resulting in a suboptimal research design for adhesion-related complications. Results from the current study show that over 65% of directly adhesion-related readmissions occur in the first 2 years after index surgery. Future studies on adhesion prevention strategies should be powered on relevant adhesion-related outcome parameters and should focus on long -term follow-up to determine the true effect on the burden of adhesions.



**Conclusion**

Laparoscopic surgery is associated with a decrease in adhesion-related readmissions. However, the incidence of adhesion-related readmissions remains high, even in laparoscopic colorectal surgery. The risk of adhesion-related readmissions in particular was determined by the extent of the surgical procedure (either open or laparoscopic). In multivariate analysis laparoscopic surgery was associated with a decrease in adhesion-related readmission rates (HR 0.52), while more extended colorectal surgical procedures and female sex were associated with an increase in adhesion-related readmission rates.

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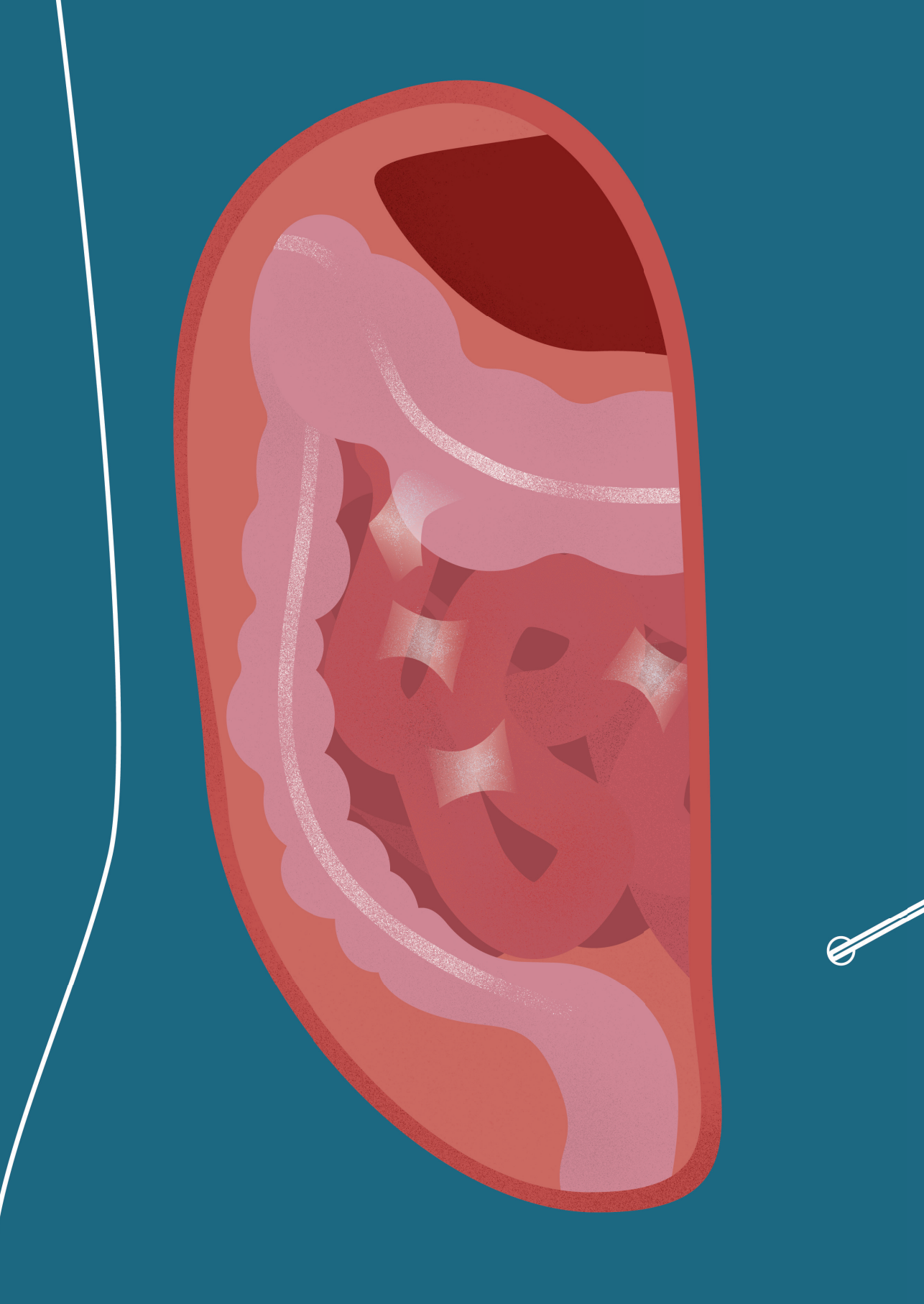
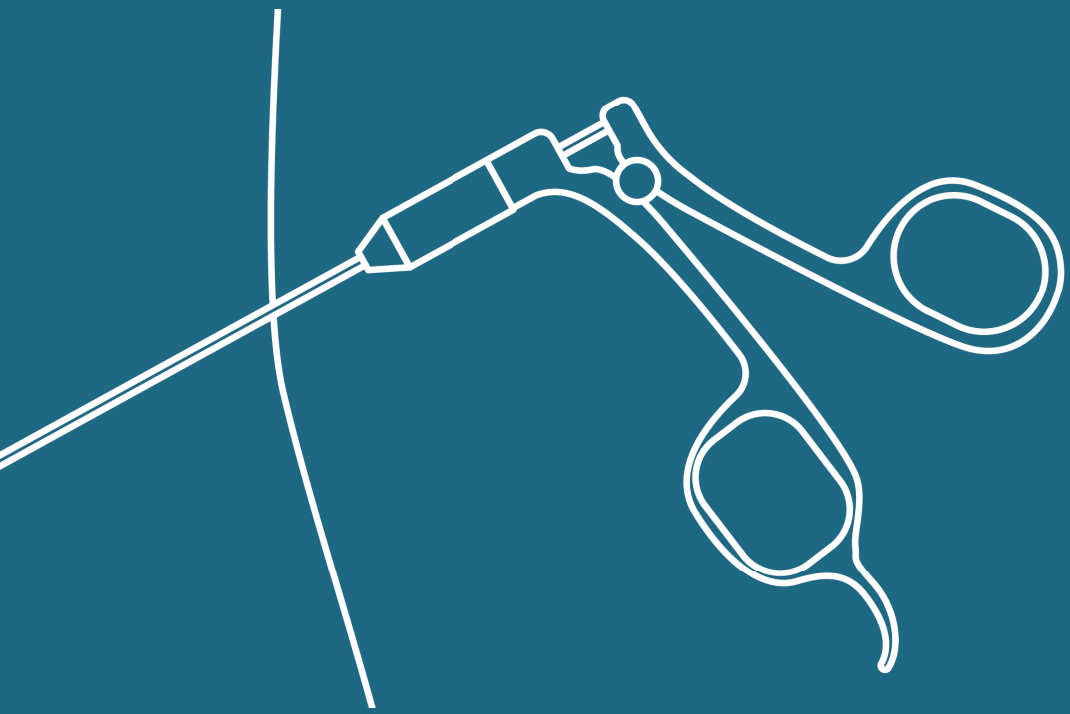


# 4

# In-hospital costs of an admission for adhesive small bowel obstruction



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**Abstract**

*Background*

Previous research on the costs of treatment for ASBO is outdated and often based on reimbursements, rather than true healthcare provider costs of the admission and related interventions. An accurate estimate of the true costs of treatment is necessary to understand the healthcare burden and to model cost-efficacy of adhesion strategies. The aim of this study was to provide an accurate cost estimate of the in-hospital costs for treatment of adhesive small bowel obstruction (ASBO) using micro-costing methods.

*Methods*

Consecutive patients admitted for ASBO to the Radboud University Medical Center from November 2013 to November 2015 were included. An episode of ASBO was defined as an admission for SBO with operative confirmation of adhesions or after radiological exclusion of other causes for SBO. For the purpose of generalization we used the costs of medication and interventions as provided by the Dutch Healthcare Authority and only if these were not available local hospital costs. We evaluated costs separately for operative and non-operative treatment for ASBO.

*Results*

During the study period 39 admissions for ASBO were eligible for analysis. An operative treatment was required in 19 patients (48.7 %). Mean hospital stay for ASBO with operative treatment was 16.0 ± 11 days versus 4.0 ± 2.0 days for non-operative treatment (P = 0.003). A total of 12 patients developed complications, 2 in the non-operative group (10 %) and 10 in the operative group (52.6 %; P = 0.004). Overall costs for an admission for ASBO with operative treatment were €16 305 (SD €2 513), and for non-operative treatment € 2 277 (SD € 265) (p = <0.001). The highest expenditure with operative treatment for ASBO was made for ward stay (mean €7 856, SD €6 882), OR time (mean €2 6845, SD €1 434), ICU stay (mean €2 183, SD €4 305) and (parenteral) feeding costs (mean €1 797, SD €2 070). A table with correction coefficient to correct for differences in price levels for goods and services between different countries has been added.

*Conclusion*

The in-hospital costs of an admission for ASBO are higher than previously thought. These costs can be used to guide hospital reimbursement policy and for the development of a cost-effective model for the use of adhesion barriers.

**Background**

Adhesive small bowel obstruction (ASBO) is the most common pathology of the small bowel, and frequently results in surgical emergencies.[1] In a national audit in the UK small bowel obstructions accounted for 51 % of all emergency laparotomies.[2] In the United States both adhesiolysis and small bowel resection appeared in the top seven of emergency general surgeries, that count for 80% of morbidity and death related to emergency surgery.[3] The supplementary data from this report confirmed that small bowel obstruction was the most common diagnosis in both procedures.[3] Part of the huge burden small bowel obstructions cause to patients and the healthcare system might be preventable.[4,5]

Post-operative adhesions are the cause of small bowel obstruction in 60 % of cases.[6] Application of an adhesion barrier during the index operation can reduce the risk of adhesion formation and subsequent clinical complications of adhesions.[4] In a meta-analyses of randomized controlled trials, application of a hyaluronate carboxymethylcellulose barrier reduced the risk of reoperations for ASBO after colorectal surgery with RR 0.49, 95 % CI 0.28–0.88.[4] Despite the evidence for efficacy these barriers are seldom applied.[7] A reason why barriers are often not applied is that policy makers question their cost-effectiveness and consider routine application too expensive.[8,9] Remarkably, there is little data on the financial implications of adhesion-related complication such as ASBO that can guide policymakers in developing guidance for reimbursement, management, and prevention of this condition. The studies that modelled cost-effectiveness of adhesion barriers have used incomplete estimates or the negotiated reimbursement prices for treatment of ASBO, rather than true healthcare provider costs.[7,8,10] By using such incomplete estimates and reimbursement prices the conclusions about cost-effectiveness of barriers might be falsified. Moreover, concerns have been raised that reimbursement prices indeed are too low, resulting in a net loss for hospitals treating patients with ASBO.[11]

In a recent study, the hospital costs of patients undergoing an emergency laparotomy in general were estimated at €15 500 per patient, which is on average €7 000 more than its reimbursement.[11] The estimate was based on operating room time, ICU and hospital stay, and did not take diagnostic or medication costs into account. Thus, it may still

underestimate the actual healthcare provider costs. The costs of emergency laparotomies were also not specified for ASBO in this study.[11] More accurate and up to date data is necessary to provide a better guide to reimbursement policies, adhesion prevention, and unveil opportunities for cost reduction.

In the present study we modelled the costs of an admission for ASBO based on accurate data that in addition to the operating room times, ICU and ward stay comprised full detailed information on all relevant interventions made during the admission, including medication, parenteral feeding, imaging studies, and laboratory studies.



**Methods**

All consecutive patients admitted with ASBO to the Radboudumc between November 2013 and November 2015 were eligible for inclusion. A waiver for ethical approval was obtained by local institutional review board after review of the protocol. To identify cases, the hospitals' discharge registry was searched for patients with a reimbursement code for small bowel obstruction. The Radboudumc is a university teaching hospital in Nijmegen, the Netherlands, with complete electronic patient files. Electronic patient files of the identified records were reviewed for an admission for ASBO during the study period. ASBO was defined as an episode with operative confirmation of adhesions, or in the non-operative group as an episode of postoperative SBO in which other potential causes of bowel obstruction were excluded by appropriate means. Patients who were treated non-operatively received tube decompression and no oral feeding. Operative treatment of ASBO consisted of an explorative laparotomy with cleaving of adhesions and if necessary partial resection of small bowel. None of the patients had laparoscopic cleaving of adhesions. Complications were defined according to the criteria of the International Classification of Diseases, Tenth Revision, the National Nosocomial Infections Surveillance System, the Center for Disease Control and Prevention, or according to the decision of the senior medical staff of the department. Complications were categorized according to the Clavien-Dindo classification.[12] All complications categorized as Clavien-Dindo grade II or higher were reported.

*Costs*

The total costs of the admission were divided in nine categories: operation (materials and occupancy of operating room), medication, radiology, laboratory, microbiology, ward stay, ICU days, feeding, and blood products administered during admission. All data needed for an accurate estimate of admission costs were derived from the electronic patients file. A standardized price list from the Dutch Healthcare Authority was used for the calculation of costs for occupancy of operating room, medication, radiology, laboratory, microbiology, ward stay, ICU stay, feeding and blood products.[13] No standardized price list was available for materials used during the operation. Therefore we used local prices for operation materials instead.

The price for occupancy of the operating room was based on the total anaesthesia time, and a standardized price of €16.70 per minute. Medication costs comprised the costs of all medications prescribed during the admission. The costs of medication were updated per April 2016.[14] Costs for radiology, laboratory, microbiology were all calculated in accordance to the table provided by the Dutch healthcare authority.[13] The prices for ICU, ward stay, feeding and blood products were based on the 2015 version of the manual for costs research.[15] The costs of a day on the ICU were determined at €2 015 per day. The costs of ward stay were determined at €435 per day. The prices for ward stay and ICU comprise honorarium for medical specialists, the costs for a resident managing the ward, nursing personnel, consumable goods, housing and overhead. The ICU price also counted for expenditures on respiratory support.[15] Oral feeding was also counted for in the price of ward stay. Additional expenditures for other types of feeding, such as parenteral feeding, were calculated separately and presented under the feeding category.

The average costs of operation materials were €155 if no bowel resection was performed and €436 if bowel resection was performed. The difference in price of materials was mainly attributable to the use of stapling devices. A table of correction coefficients was added to allow for quick comparison of costs between different countries.[16] These correction coefficients are published by the European Union's statistics department (EUROSTAT) and can be used to quickly adjust prices for the differences in price levels of goods and services

between countries. Thus, these coefficient provide a rough estimate of the prices for treatment of ASBO in other countries than the Netherlands. For convenience the coefficients as published by EUROSTAT were adjusted setting the Dutch price levels as the reference standard.

*Data and statistical analysis*

Baseline data consisted of patients age, sex, Charlson comorbidity index, ASA classification and the number of previous abdominal operations. Comparison was made between patients undergoing operative treatment and non- operative treatment using a Chi-square, Fisher's exact test, independent t-test or Mann-Whitney U test where appropriate. Continuous variables are presented as means with standard deviation, or medians with interquartile range (25–75) if non-normal distribution. Dichotomous or categorical variables are presented as absolute numbers and percentages. $P < 0.05$ was considered significant. All analyses were performed using SPSS version 23.0 (Armonk, NY: IBM Corp).



**Results**

From the hospital registry we identified 185 cases with a code of SBO. We excluded 49 patients because they were not admitted but only seen on the outpatient clinic. A total of 97 admitted patients were excluded because adhesive aetiology of SBO was not confirmed (Fig. 1). Thirty-nine patients had a total of 46 admissions for ASBO during the study period. We excluded 7 admissions because patients were transferred to other hospitals for further treatment of ABSO. A total of 39 admissions of ASBO during the study period were included in the analysis (Fig. 1). Operative treatment of ASBO was required in 19 admissions (48.7%), 20 patients were managed non-operatively (51.3%). Indications for operative treatment were failure of nonoperative management in 14 patients (73.7%), suspected strangulation in 4 patients (21.0%), and 1 patient had a diagnostic laparotomy (5.2%). Patient characteristics are shown in Table 1. There were no significant differences between groups in terms of age, sex, number of previous operations, comorbidity index, or ASA classification.

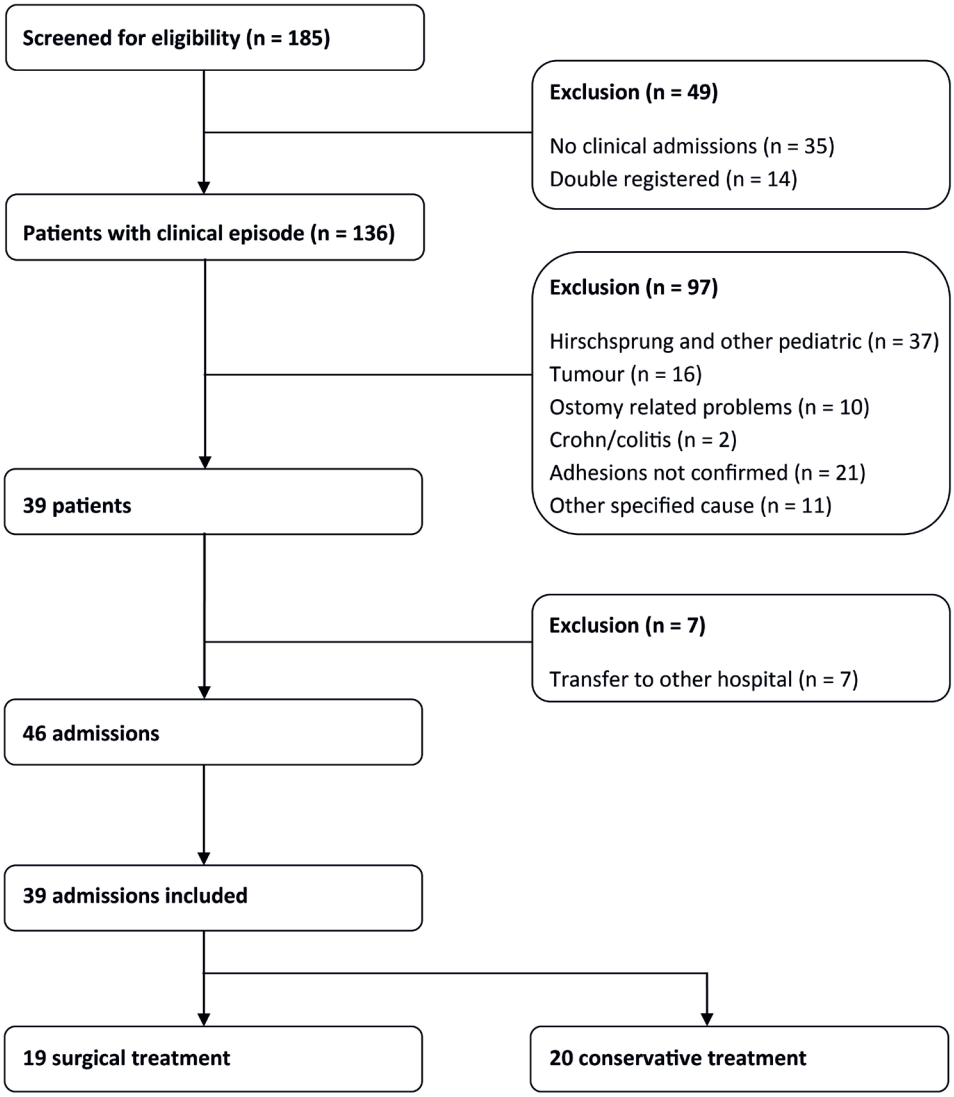


**Figure 1** Flow chart of patients included in the study

**Table 1** Baseline patient characteristics

| | Conservative treatment (n = 20) | Operative treatment (n = 19) | P-value |
|---|---|---|---|
| Age | 63.6 ± 15.7 | 63.4 ± 14.6 | 0.962 |
| Female | 12 (60.0%) | 14 (73.7%) | 0.365 |
| Previous abdominal operations [a] | 2 (IQR 2-3) | 1 (IQR 1-3) | 0.111 |
| Charlson score | 3.3 ± 2.4 | 3.6 ± 1.7 | 0.568 |
| ASA score | | | |
| Class 2 | 17 (85.0%) | 16 (84.2%) | 0.946 |
| Class 3 | 3 (15.0%) | 3 (15.8%) | |
| Origin | | | |
| Home | 19 (95.0%) | 19 (100%) | 0.336 |
| Nursing home | 1 (5.0%) | 0 (0.0%) | |

Values are presented as mean ± standard deviation or N (percentage)

[a] median + inter quartile range (IQR)

Of 19 operated patients, 9 were operated within the first 24 h. Median time from admission till operation was 2 days (IQR 1–4 days). One patient was operated after 16 days. This patient had developed an adhesive small bowel obstruction after a previous appendectomy, during late pregnancy. She was treated with parenteral feeding and had explorative laparotomy delayed to be combined with caesarean section at 32 weeks of gestational age. Her bowel obstruction quickly resolved after laparotomy, and mother and child were discharged in good condition 4 days after surgery.

Operative treatment of ASBO led to a mean hospital stay of 16.0 days (SD 11.0 days) while non-operative treatment of ASBO led to a mean hospital stay of 4.0 days (SD 2.0 days P = 0.003). A total of 12 patients developed complications, two in the non-operative group (10.0 %) and 10 in the operatively treated group (52.6 %; P = 0.004). Complications in the non- operative group were pneumonia (n = 1), and de novo atrial fibrillation (n = 1). One

patient in the operative group developed a staphylococcal sepsis, for which prolonged ICU admission was indicated. Other complications in the operative group comprised pneumonia (n = 2), wound infection (n = 2), intra-abdominal abscess formation (n = 1), de novo atrial fibrillation (n = 1), urinary tract infection (n = 1), bacteremia (n = 1), and delirium (n = 1). Two operative patients had a second-look laparotomy. In the first patient almost the entire small bowel was entrapped in the adhesions and appeared ischemic at the initial explorative laparotomy. Because there was doubt about the reversibility of this bowel ischemia a second look laparotomy was performed the next day, at which the bowel had normal appearance and peristalsis. The second patient underwent a second look laparotomy to inspect the anastomosis made following bowel resection at initial laparotomy. The indication for this second look was made after the patients became septic on the ICU and an anastomotic leakage was expected based on clinical evaluation. At second look on day 3 a sufficient anastomosis without signs of leakage was found. Origin of sepsis remained unsure, but a pulmonary origin was suspected after negative second look. The patient fully recovered with intravenous antibiotic treatment.

*Costs*

Mean hospital stay for ASBO with operative treatment was 16.0 ± 11 days versus 4.0 ± 2.0 days for non-operative treatment (P = 0.003), resulting in a mean overall costs of €16 305 (SD €2 513) and €2 277 (SD €265) respectively. Mean costs were significantly different between both groups (P < 0.005). Costs of the different components are shown in Table 2. For both treatment strategies, ward and ICU stay were the largest component of costs (Fig. 2). The costs for operative treatment were €14 315 (SD €3 352) in uncomplicated cases and €18 095 (SD €3 776) in complicated cases, the difference was not significant. Four of the patients in the operative treatment group underwent bowel resection during laparotomy (21.5%). Mean costs were significantly different between operative treatment with or without bowel resection, €25 395 versus €13 058 respectively. The additional operative costs for second look laparotomy in two patients were € 601 and €1 319 respectively.

*Correction coefficients*

An overview of correction coefficients is presented in Table 3. The correction coefficients give a global impression of differences in price levels between countries, and were standardized to the Dutch price levels. For example the correction coefficient for the United Kingdom is 1.29. This means that prices for goods and services in the United Kingdom are generally 1.29 times higher than the costs for the same goods and services in the Netherlands. The price for a non-operative treatment for ASBO in the United Kingdom are roughly estimated at 1.29*€ 2 227 = €2 872.

**Table 2** Comparison of costs for operative vs. non-operative management for ASBO

| | Operative | | Non-operative | | P-value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Operation - anesthesia time | € 2 684.71 | € 1 434.29 | NA | NA | NA |
| Operation - materials | € 259.90 | € 148.74 | NA | NA | NA |
| Medication | € 634.13 | € 816.08 | € 99.34 | € 93.17 | P = 0.011 |
| Feeding | € 1 797.37 | € 2 069.71 | € 91.65 | € 288.56 | P < 0.005 |
| Blood products | € 31.74 | € 100.79 | NA | NA | NA |
| Radiology | € 510.00 | € 467.70 | € 154.92 | € 159.88 | P < 0.005 |
| Laboratory | € 324.49 | € 223.20 | € 69.82 | € 38.94 | P < 0.005 |
| Microbiology | € 69.70 | € 98.10 | € 11.06 | € 37.34 | P = 0.023 |
| Ward | € 7 855.74 | € 6 881.54 | € 1 850.47 | € 913.92 | P < 0.005 |
| ICU | € 2 183.00 | € 4 304.93 | NA | NA | NA |
| Total | € 16 304.92 | € 2 513.07 | € 2 277.27 | € 265.34 | P < 0.005 |



**Discussion**

Adhesive small bowel is associated with high morbidity and costs. The average costs for a non-operative episode were over €2 000 and for a surgical episode over €16 000. The majority of costs were related to ward and ICU stay. The costs for operative treatment of ASBO determined in this study were comparable to the €15 500 Shapter et al. reported in their estimation of the costs for an unspecified emergency laparotomy.[11] In their study, the costs for an emergency laparotomy were estimated from only the ICU stay, hospital stay, and duration of the operation. In our study these three parameters made up for only

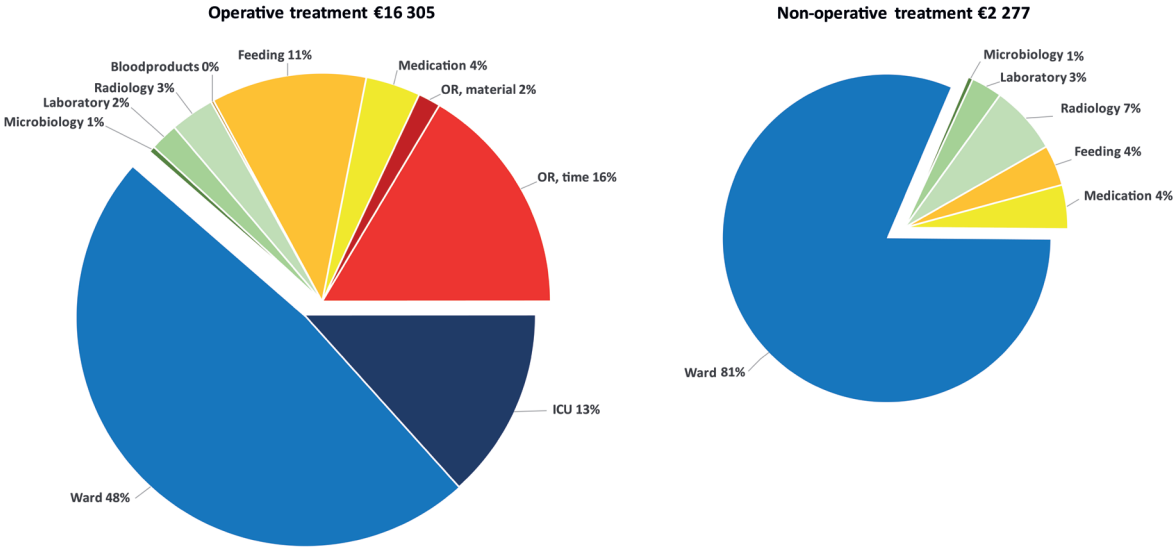


**Figure 2** Pie chart of treatment costs for ASBO

77% of total hospital costs in operative cases, indicating that Shapter's estimate is too low. Local differences in price levels between the United Kingdom and the Netherlands might account for the discrepancy, implicating that true costs in the United Kingdom are higher. Indeed the correction coefficient for the United Kingdom was 1.29, indicating that goods and services are generally more expensive in the United Kingdom as compared to the Netherlands. The most important additional expenditure in operative patients is the costs for parenteral feeding. Parenteral feeding made up for 11% of total healthcare costs in our group. The costs for operative treatment of ASBO are much higher than reimbursements for emergency laparotomies found by Shapter et al., implicating that hospitals in the United Kingdom bear a financial loss for treating patients with ASBO.[11]

Correction coefficients can be used to calculate a quick estimate of the costs in a different country. However, a more precise estimate would require to recalculate the prices from the different components as listed in Table 2. An important limitation to the correction coefficients is that they are not specific for healthcare services.[16] Attempts to create more specific coefficients for healthcare have been complicated by the fact that for most condition not only the price levels of goods and services vary between countries, but also the treatment protocols itself.[17] However, we believe that it is reasonable to suggest that

**Table 3** Correction coefficients for differences in prizes of goods and surfaces

| Country | Correlation coefficient |
|---|---|
| Netherlands | 1.00 |
| Australia | 0.96 |
| Austria | 0.98 |
| Belgium | 0.96 |
| Bulgaria | 0.51 |
| Canada | 0.99 |
| Croatia | 0.67 |
| Cyprus | 0.80 |
| Czech Republic | 0.65 |
| Denmark | 1.24 |
| Estonia | 0.76 |
| Finland | 1.09 |
| France | 1.00 |
| Germany | 0.92 |
| Greece | 0.76 |
| Hungary | 0.60 |
| Ireland | 1.03 |
| Israel | 1.04 |
| Italy | 0.93 |
| Latvia | 0.69 |
| Lithuania | 0.64 |
| Luxembourg | 0.96 |
| Malta | 0.82 |
| Poland | 0.61 |
| Portugal | 0.77 |
| Romania | 0.56 |
| Slovakia | 0.67 |
| Slovenia | 0.75 |
| Spain | 0.86 |
| Sweden | 1.12 |
| United Kingdom | 1.29 |
| United States | 1.05 |

Source: Eurostat (http://ec.europa.eu/eurostat/web/civil-servants-remuneration/correction-coefficients)

The correlation coefficients give a general estimate for the differences in price level in different countries

differences in ASBO treatment decreasing over recent years by the use of international guidelines. Adherence to the international Bologna guidelines for treatment of ASBO in this study was high.[1] As a rule, a non-operative treatment was initially instigated, unless there were signs of strangulation or ischemia. Most operative patients underwent surgery within 3 days as suggested by these guidelines.

The cost estimates in our study are useful to guide reimbursement policies and model cost-effectiveness of adhesion barriers. The study had a high adherence to the international guidelines and the morbidity found was comparable with reported morbidity in literature.[6,11,18,19] However, the retrospective nature of the study and its low power impaired analyses of the impact of factors such as complications on costs.

The relative small sample size is explained by the methodology used in this study. We included only recently admitted patients from our own institution with high ascertainment of adhesive etiology to enable the micro-costing method. Micro-costing is the gold standard for accurately defining healthcare provider costs, but seldom applied because of the large quantity of data that needs to be collected from each patient.[15] In our institution all patient data, including medication, radiology orders etc. are entered into the electronic patient file, which enabled this highly accurate method of cost estimation. For the same reasons the number of patients undergoing operative treatment was relative high in our cohort. In previous literature, non-operative treatment is successful in more than 70% of patients with ASBO.[20,21] We only included patients with high ascertainment of adhesive aetiology and in many of the non-operative cases the presence of adhesions could not be proved. We included only patients with high ascertainment of ASBO in this study because costs rather than treatment result was the primary endpoint. Without additional imaging or a history of previous episodes of ASBO, adhesions count for only 60% of all cases of post-operative bowel obstruction.[6] The other 40 % might have somewhat different clinical course and costs.

We also excluded a larger number of paediatric patients with Hirschsprung's disease. Our Institution is also a referral central for paediatric surgery. Because Hirschsprung's disease

has no separate reimbursement code in the Dutch reimbursement system, it often received the same code as used for bowel obstruction.[22]

Our results show that the largest part of the expenditures in treatment of ASBO are related to the duration of hospital stay. Several studies have reported a reduced length of stay and lower incidence of postoperative ileus when adhesiolysis is performed through laparoscopy instead of laparotomy.[23-25] However, no randomized trials have been performed. In general, it will be more difficult to perform laparoscopic surgery on patients with multiple operations in history and when the bowel is very distended, increasing the risk of bowel injuries.[26] In the study of Wullstein et al. incidence of bowel injuries was higher during laparoscopic surgery for ASBO compared with open surgery, despite a possible favourable selection in laparoscopic cases.[24] Thus, the results that laparoscopic surgery for ASBO reduces hospital stay and subsequent costs should be interpreted with caution.



The results of our study have important implications for policies regarding reimbursements. Reimbursement for operative cases of ASBO is generally too low.[11] The costs that we found for operatively treated episodes of ASBO were also much higher than the estimate Wilson applied in a cost-effectiveness model for adhesion barriers.[8] With the higher costs we found for operative cases of ASBO, it becomes more likely that adhesion barriers are cost effective in high risk procedures such as colorectal surgery. Adhesion barriers are proven to be effective in reducing the risk of reoperation for ASBO in randomized controlled trials.[4,5,27,28] Moreover, a complete evaluation of cost-effectiveness of adhesion barriers should also count for other complications of adhesions, such as complications associated with adhesiolysis during repeat abdominal surgery, infertility treatments and chronic abdominal pain.[8,10]

**Conclusion**

The costs of an admission for ASBO are higher than reported in the previous literature. Our results can be used to guide reimbursement policy and the development of a cost-effectiveness model for the use of adhesion barriers.

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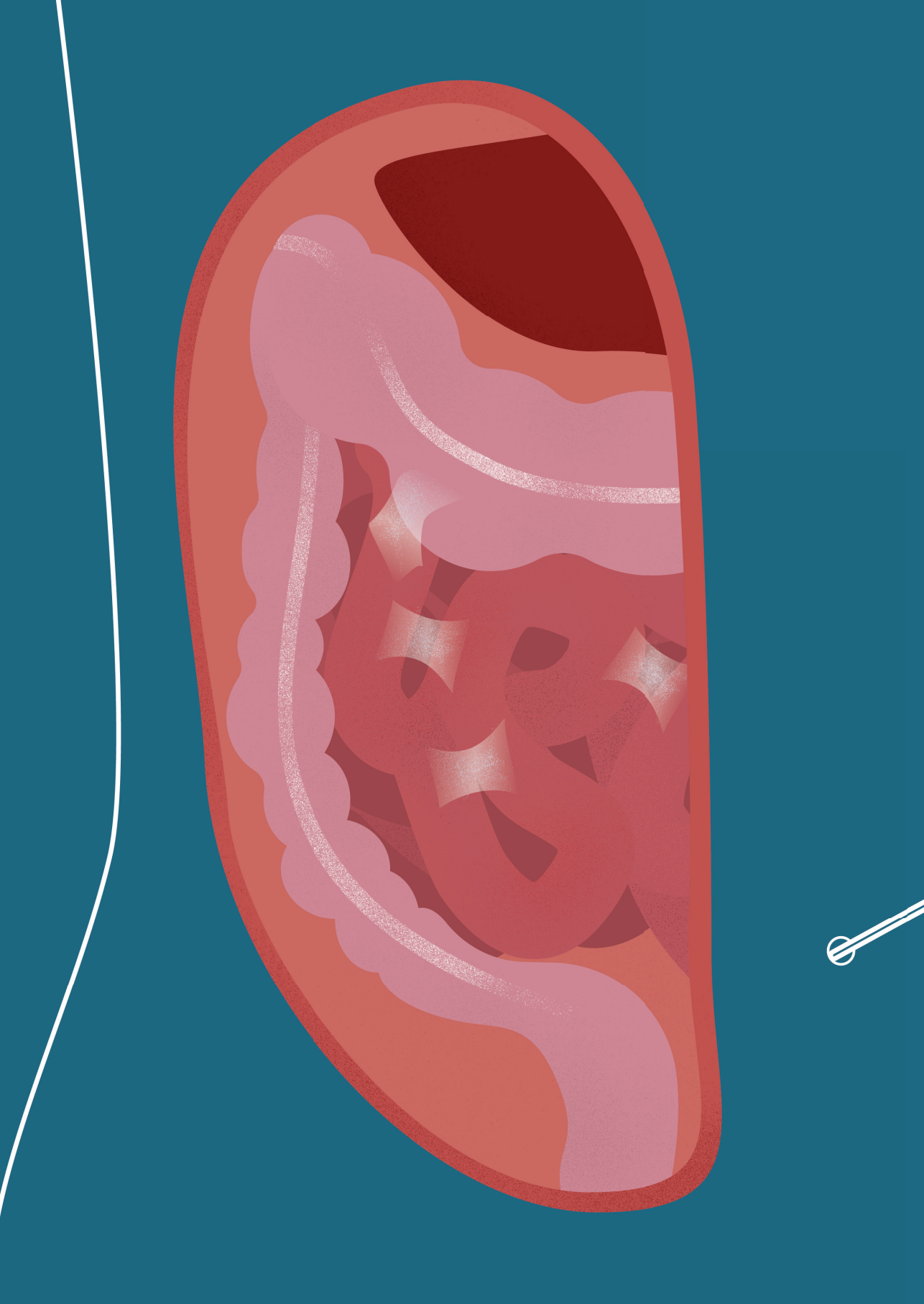

# 5

# Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group

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**Abstract**

*Background*

Adhesive small bowel obstruction (ASBO) is a common surgical emergency, causing high morbidity and even some mortality. The adhesions causing such bowel obstructions are typically the footprints of previous abdominal surgical procedures. The present paper presents a revised version of the Bologna guidelines to evidence based diagnosis and treatment of ASBO. The working group has added paragraphs on prevention of ASBO and special patient groups.

*Methods*

The guideline was written under the auspices of the World Society of Emergency Surgery by the ASBO working group. A systematic literature search was performed prior to the update of the guidelines to identify relevant new papers on epidemiology, diagnosis, and treatment of ASBO. Literature was critically appraised according to an evidence-based guideline development method. Final recommendations were approved by the workgroup, taking into account the level of evidence of the conclusion.

*Recommendations*

Adhesion formation might be reduced by minimally invasive surgical techniques and the use of adhesion barriers. Non-operative treatment is effective in most patients with ASBO. Contraindications for non-operative treatment include peritonitis, strangulation, and ischemia. When the adhesive etiology of obstruction is unsure, or when contraindications for non-operative management might be present, CT is the diagnostic technique of choice. The principles of non-operative treatment are nil per os, naso-gastric, or long-tube decompression, and intravenous supplementation with fluids and electrolytes. When operative treatment is required, a laparoscopic approach may be beneficial for selected cases of simple ASBO. Younger patients have a higher lifetime risk for recurrent ASBO and might therefore benefit from application of adhesion barriers as both primary and secondary prevention.

*Discussion*

This guideline presents recommendations that can be used by surgeons who treat patients with ASBO. Scientific evidence for some aspects of ASBO management is scarce, in particular aspects relating to special patient groups. Results of a randomized trial of laparoscopic versus open surgery for ASBO are awaited.

**Background**

Adhesive small bowel obstruction (ASBO) is one of the leading causes of surgical emergencies and in particular of surgical emergencies that require an emergent operations.[1-4] In the UK, small bowel obstruction was the indication for 51% of all emergency laparotomies.[2] Scott et al. reported on seven emergency surgical procedures that account for 80% of all general surgery emergency admissions, morbidity, deaths, and healthcare expenditures in the USA.[3] Adhesive small bowel obstruction was the most common diagnosis for both the top 2 (small bowel resection) and top 5 (adhesiolysis) procedures.[3] Post-operative adhesions are the leading cause of small bowel obstructions, accounting for 60% of cases.[1]

ASBO causes considerable harm, resulting in 8 days of hospitalization on average and an in-hospital mortality rate of 3% per episode.[5-8] Between 20 and 30% of patients with adhesive small bowel obstruction require operative treatment.[1,9-11] Length of hospitalization and morbidity depend on the need for surgical intervention. Average hospitalization after surgical treatment of ASBO is 16 days, compared to 5 days following non-operative treatment.[12] Associated costs in a Dutch study in 2016 were estimated at €16 305 for surgical and €2 227 for non-operative treatment.[12]

Although adhesive small bowel obstruction is a common condition, the prevention and treatment is often characterized by surgeons' personal preferences rather than standardized evidence-based protocols. There is a large amount of conflicting and low-quality evidence in publications regarding treatment of adhesive small bowel obstruction.

Therefore, the World Society of Emergency Surgery (WSES) working group on ASBO has developed evidence-based guidelines to support clinical decision making in diagnosis and management of ASBO.[11,13] In the present revision of these guidelines, all recommendations were updated according to the latest evidence available from the medical literature. Further, we have introduced two new sections: prevention of ASBO and special patient groups.

**Methods**

The guideline was written under the auspices of the WSES by the ASBO working group. Systematic searches of the MEDLINE and Embase databases were carried out in October 2016 using the keywords relevant to each section. Terms relevant to each section of the guideline were mapped to MEDLINE Medical Subjects Headings (MeSH) terms, as well as searched for as text items. Articles describing randomized controlled trials and systematic reviews were searched for using the methodological filters of the Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk/methodological-principles.html). The bibliographies of included articles were subsequently hand-searched for other relevant references, and experts in the field were asked if they found any relevant reports missing.

*Critical appraisal*

Articles selected to support recommendations were assessed using the levels of evidence as published by the Centre for Evidence-Based Medicine of the University of Oxford (www.cebm.net; Table 1). Articles were classified according to the type of article and individually assessed for methodological quality using the GRADE method as proposed by the GRADE working group. That working group has developed a common, sensible, and transparent approach to grading the quality of evidence and strength of recommendations (http://www.gradeworkinggroup.org). The main literature on which the conclusion for each relevant topic is based is stated with the conclusion, accompanied by the level of evidence (Table 2).[14,15]

Conclusions and recommendations are graded according to the level of evidence from strong ("there is strong evidence for," level A) to weak ("we cannot be confident," level D). Recommendations were graded as strong recommendations (level I) or weak recommendation or suggestions (level II). Recommendations were considered strong recommendations if there is sufficient evidence (level A or B) demonstrating that the benefits of an intervention are of clinical importance and clearly outweigh the harm of the intervention. A concept guideline was sent to all involved for comment and approval after which internal consensus was reached between the members of the working group.

Amendments were made based upon these comments, leading to the final version of this updated guideline.

*Definitions*

Peritoneal adhesions

The term “peritoneal adhesions” or simply “adhesions” is defined as fibrous tissue that connects surfaces or organs within the peritoneal cavity that are normally separated. Such adhesions are the results of a pathological healing response of the peritoneum upon injury, as opposed to the normal “ad integrum” repair.[16] Typical adhesions form after peritoneal injury from abdominal surgery. Other conditions that may cause peritoneal injury resulting in adhesion formation include radiotherapy, endometriosis, inflammation, and local response to tumors. Adhesions from a non-operative etiology are often part of a more complex pathology that can cause chronic pain and complications as the result of adhesions and other mechanisms.[17] Management of chronic abdominal complications by adhesiolysis is controversial.[18,19] The scope of the present guideline is limited to diagnosis and management of acute bowel obstructions.

Adhesive small bowel obstruction

Small bowel obstruction is a surgical emergency in which the obstruction of the small intestine hinders passage of intestinal contents. Small bowel obstruction is characterized by abdominal pain, vomiting, distention, and constipation. Adhesions are the single most common cause for small bowel obstruction.[1,20] Nonadhesive etiologies of bowel obstruction include incarcerated hernias, obstructive lesions (malignant and benign), and a number of infrequent causes for bowel obstruction such as bezoars, inflammatory bowel disease, and volvulus.[21-25] Definitive confirmation of the adhesive etiology of bowel obstruction is made during operative treatment. Methods to confirm the adhesive etiology of bowel obstruction non-invasively include a history of previous episodes of bowel obstruction by adhesions or exclusion of other causes of bowel obstruction by imaging (often CT scan).

**Table 1** Classification of evidence per article

| Level of evidence | Interventional research | Studies concerning diagnostic accuracy |
|---|---|---|
| A1 | Systematic review/meta-analysis of at least 2 independently performed level A2 studies | |
| A2 | Double-blind controlled randomized comparative clinical trial of good study quality with an adequate number of study participants | Diagnostic test compared to reference test; criteria and outcomes defined in advance; assessment of test results by independent observers; independent interpretation of test results; adequate number of consecutive patients enrolled; all patients subjected to both tests |
| B | Comparative studies, but without all the features mentioned for level A2 (including patient-control studies, cohort studies) | Diagnostic test compared to reference test, but without all the features mentioned in A2 |
| C | Noncomparative studies | |
| D | Expert opinion | |



Adhesiolysis

Adhesiolysis refers to releasing adhesions either by blunt or sharp dissection during surgery. It can be the primary indication for an operation, as in a reoperation for small bowel obstruction caused by adhesions. Adhesiolysis is also performed during reoperations for indications not related to adhesions in order to obtain sufficient access to the operative field. Complicated adhesiolysis refers to the event of inadvertent injury while performing adhesiolysis. Injuries during adhesiolysis are most frequently made to the bowel. These bowel injuries are classified as:

– Seromuscular injury: injury to the visceral peritoneum (serosa) and smooth muscle layer of the bowel. The lumen of the bowel or leakage of bowel contents is not visible.

– Enterotomy: a full thickness injury to the bowel. The mucous layer or lumen of the bowel is visible, or there may be leakage of intestinal contents.

– Delayed diagnosed perforation: bowel injuries made during surgery that initially go unrecognized. Typically, the abdomen is closed at the end of procedure with the bowel injury still in place, causing patients to deteriorate during the postoperative course.

**Table 2** Grading of the conclusions and recommendations according to the level of evidence and strength of recommendation

| Level | Conclusion based on |
|---|---|
| **A** | Systematic review (A1) or at least 2 independent studies with evidence level A2<br>('there is evidence that …') |
| **B** | One study with evidence level A2 or at least 2 independent studies with evidence level B<br>('it is likely that …') |
| **C** | One study with evidence level B or level C<br>('there are indications that …') |
| **D** | Expert opinion<br>('the working group recommends …') |

| Level | Recommendation |
|---|---|
| **I** | Strong recommendation |
| **II** | Weak recommendation (suggestion) |

**Results**

*Epidemiology*

The risk of SBO is highest following colorectal, oncologic gynecological, or pediatric surgery.[1,26-28] One in ten patients develops at least one episode of SBO within 3 years after colectomy.[7] Reoperations for ASBO occur in between 4.2 and 12.6% of patients after pediatric surgery patients, and 3.2% of colorectal patients.[1,29] Recurrence of ASBO is also frequent; 12% of non-operatively treated patients are readmitted within 1 year, rising to 20% after 5 years. The risk of recurrence is slightly lower after operative treatment: 8% after 1 year and 16% after 5 years.[30]

*Classification of adhesions*

The most frequently used classification of adhesions in general surgery is the adhesion score according to Zühlke et al. (Table 3).[31] The score is based on the tenacity and some morphologic aspects of the adhesions. The merits of this score are that it is easy to use and classifications are self-explanatory to most surgeons and gynecologists. The major drawback to the score is that it does not measure the extent of adhesions and that tenacity of adhesions can vary between different parts of the abdomen. The most used grading system in gynecological surgery is the American Fertility Society (AFS) score.[32] The score is designed for grading adhesions in the small pelvis. Adhesions are scored for extent and severity at four sites: right ovary, right tube, left ovary, and left tube. The scores for the right and left side are summed, and the final AFS score is the score for the side with the lowest summed score while discarding the score for the other side. Thus, a patient with an AFS score of 0 can still have adhesions. Further critiques for this score include a relatively low inter-observer reproducibility.[33] A modified AFS has therefore gained popularity in more recent studies.[34]

A recently introduced score by the ASBO working group is the peritoneal adhesion index (PAI), which measures tenacity on a 1–3 scale at 10 predefined sites, to integrate tenacity and extent of adhesions in a single score (Fig. 1).[35] This score is the only score that has been validated to be prognostic for convalescence after surgery for ASBO and the risk of injuries

during adhesiolysis.[36] A limitation to all these adhesion scores is that they are only applicable to operative cases because they require operative assessment. Furthermore, none of them has yet been validated to correlate with the long-term risk for (recurrence of) adhesion-related complications.

**Table 3** Classification of adhesions according to Zühlke et al.

| Grade | Definition |
|---|---|
| 0 | No adhesions or insignificant adhesions |
| 1 | Adhesions that are filmy and easy to separate by blunt dissection |
| 2 | Adhesions where blunt dissection is possible but some sharp dissections necessary, beginning vascularization |
| 3 | Lysis of adhesions possible by sharp dissection only, clear vascularization |
| 4 | Lysis of adhesions possible by sharp dissection only, organs strongly attached with severe adhesions, damage to organs hardly preventable |

A different type of classification in the field of ASBO is risk stratification that predicts the need for surgery. Zielinski reported on three radiological and clinical signs that correlate with the need for surgical exploration: mesenteric edema, absence of the small-bowel feces sign, and obstipation. The score was validated in 100 cases of ASBO and predicted the risk with a concordance index of 0.77.[37] A more accurate model was reported by Baghdadi et al. This score comprises radiological findings, sepsis criteria, and comorbidity index. Although the score is somewhat complex to assess, it correlates with an area under the curve of 0.80 in a validation study of 351 cases.[38]

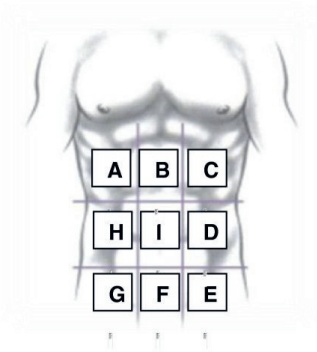
*Prevention*

Surgical technique

The main principles of prevention of adhesions and related complications are minimizing surgical trauma and the use of adjuvants to reduce adhesion formation. Laparoscopy is often believed to reduce adhesion formation and the risk for ASBO. In a systematic review of cohort studies, the incidence of reoperation for ASBO was 1.4 (95% CI 1.0–1.8%) after laparoscopic and 3.8% (95% CI 3.1–4.4%) after open surgery. However, there were

differences in both the type and indications for surgery.[1] In a recent meta-analysis of SBO after colorectal operations, the incidence of ASBO after laparoscopic surgery was somewhat lower than after open colorectal procedures (OR 0.62, 95% CI 0.54 to 0.72). However, no significant difference was found in the three randomized trials included in this review (OR 0.50, 95% CI 0.20 to 1.20).[39] In summary, there is some evidence that the incidence of ASBO is lower after laparoscopy. However, the effect seems modest when correcting for type and indication of surgery. Thus, performing (colorectal) surgery by laparoscopy is not a complete solution to preventing adhesive SBO.

## PERITONEAL ADHESION INDEX:




| Regions: | Adhesion grade: | Adhesion grade score: |
|---|---|---|
| **A** Right upper | ____ | **0** No adhesions |
| **B** Epigastrium | ____ | **1** Filmy adhesions, blunt dissection |
| **C** Left upper | ____ | **2** Strong adhesions, sharp dissection |
| **D** Left flank | ____ | **3** Very strong vascularized adhesions, sharp |
| **E** Left lower | ____ | dissection, damage hardly preventable |
| **F** Pelvis | ____ | |
| **G** Right lower | ____ | |
| **H** Right flank | ____ | |
| **I** Central | ____ | |
| **L** Bowel to bowel | ____ | |

**PAI** ☐

**Figure 1** Peritoneal adhesion index. Reproduced with permission[35]

Many other aspects of surgical technique have been associated with adhesion formation, although there are little or no epidemiological data concerning their impact on the incidence of ASBO. Nevertheless, a number of important risk factors for aggravated adhesion formation are worth considering. One of the most important risk factors is the foreign body reaction, for example as seen with starch-powdered gloves, and meshes used for abdominal wall reconstruction.[40,41] The choice of energy device might also impact adhesion formation. Peritoneal injury is lower in bipolar electrocautery and ultrasonic devices as compared to monopolar electrocautery.[42,43] Animal data suggest that both systemic and intraperitoneal application of antibiotics, and metronidazole in particular, can reduce adhesion formation in septic conditions.[44,45]

Adhesion barriers

Adhesion barriers are adjuvants for peritoneal administration that can effectively reduce adhesion formation. Adhesion barriers are produced in several forms: solid membranes, gels, and liquids. The concept behind barriers is that they do not actively interfere with inflammation and wound healing. Rather, they act as a spacer which separates injured surfaces of the peritoneum, allowing these surfaces to heal without forming fibrinous attachments which eventually lead to adhesions. In order to accomplish this task, such barriers should ideally be inert to the human immune system and be slowly degradable.

There is moderate evidence that a hyaluronate carboxymethylcellulose adhesion barrier can reduce the incidence of reoperations for ASBO in colorectal surgery. In three trials involving 1132 patients undergoing colorectal surgery, hyaluronate carboxymethylcellulose reduced the incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28–0.88).[46-48] The use of such barriers seems cost-effective in open colorectal surgery.[49] An overview of common used adhesion barriers and their efficacy is found in Table 4.

*Secondary prevention*

Adhesion barriers might also be useful to prevent recurrence after surgical treatment of ASBO. One randomized trial with an adhesion barrier included patients undergoing surgery for ASBO.[20] In this trial, patients were randomized to a liquid 4% icodextrin adhesion barrier

**Table 4** Overview of most common applied adhesion barriers and their impact on adhesion formation and incidence of ASBO

| Barrier | Marketed as | Comments |
|---|---|---|
| Hyaluronate carboxymethylcellulose | Seprafilm® | Solid barrier most suitable for open surgery although laparoscopic placement have been described.<br>Studies in both general surgery and gynecological procedures.<br>Reduces adhesions formation, as well as the risk for reoperations for adhesive small bowel obstruction (relative risk 0.49, 95% CI 0.28–0.88). |
| Oxidised regenerated cellulose | Interceed® | Solid barrier most suitable for open surgery<br>Only studied in gynecological procedures<br>Reduces incidence of adhesion formation relative risk 0.51, 95% CI 0.31–0.86.<br>No studies available on subsequent risk of ASBO.<br><br>This workgroup does not recommend use of this barrier to prevent ASBO in general surgery. |
| Icodextrin | Adept® | Liquid barrier, easy to apply in both open and laparoscopic surgery.<br>Good safety record in both general surgery and gynecological surgery.<br>Reduces recurrence of ASBO following surgery for ASBO in one trial (relative risk 0.20, 95% CI 0.04–0.88). |
| Polyethylene glycol | Sprayshield®/ Spraygel® | Gel barrier, easy to apply in both open and laparoscopic surgery.<br>Reduces adhesion score in both general surgery and gynecological trials.<br>Relative few and small studies, impact on long-term adhesion related complications not described. |

Adapted from: ten Broek, Stommel MWJ, Strik C, et al. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. Lancet. 2014 Jan 4;383(9911):48-59.

or standard operative treatment without an adhesion barrier. The ASBO recurrence rate was 2.19% (2/91) in the icodextrin groups versus 11.11% (10/90) in the control group after a mean follow-up period of 41.4 months ($p < 0.05$).[20] In this trial, the barrier was applied in patients treated for ASBO by laparotomy. However, the icodextrin 4% adhesion barrier can also be administered in laparoscopic surgery. Other trials with icodextrin as an adhesion barrier indicated that it actually might not be the most potent barrier to prevent adhesion reformation, which is typically more challenging than prevention of de novo adhesions.[50] Favoring the use of icodextrin are its low costs and good safety record.[51] From the results of other trials, we suggest that a hyaluronate carboxymethylcellulose might be more efficacious, but this barrier is less practical in laparoscopic surgery.[46–48,52]

*Approach to the patient with ASBO*

An algorithm for the diagnostic and therapeutic approach to the patient with ASBO is presented in Fig. 2. The initial diagnosis of ASBO is of utmost importance. Failure to diagnose or having a delayed diagnosis represents 70% of malpractice claims in ASBO.[53,54]

The primary goals in the initial evaluation of patients in whom adhesive small bowel obstruction is suspected are:

– Differentiating between adhesive small bowel obstruction and other causes of bowel obstruction

– Assessing the need for urgent surgical exploration

– Identifying and preventing complications from bowel obstruction

History taking and physical examination

History taking in a patient suspected for ASBO includes assessment of potential causes of bowel obstruction (previous operations, radiotherapy) and nutritional status. Signs of dehydration should also be assessed. Traditionally, ASBO is clinically diagnosed in a patient with intermittent colicky abdominal pain, distention, and nausea (with or without vomiting), with or without absence of stools. Although diagnosis of small bowel obstruction is fairly

certain in a patient in whom all of these symptoms are present, there are some specific pitfalls that can result in delayed or misdiagnosis of bowel obstruction upon initial presentation. In patients with incomplete obstruction, watery diarrhea may be present. The presence of watery diarrhea can cause an episode of ASBO to be mistaken for gastro-enteritis. Stool might also be present in patients with a relatively high obstruction who are admitted early after onset of symptoms. Moreover, not all of these symptoms may be present, especially in the elderly in whom pain is often less prominent.[55,56]

During physical examination, signs of peritonitis that might reveal strangulation or ischemia should be evaluated. Differential diagnostic considerations that can be assessed during physical examination include the presence of any abdominal wall or groin hernias. The evaluation of ASBO by history taking and physical examination has a low sensitivity for detecting bowel strangulation and ischemia. Sensitivity of physical examination for detection of strangulation is only 48%, even in experienced hands.[57]



Laboratory test

The minimum of laboratory tests include blood count, lactate, electrolytes, CRP, and BUN/creatinine. Laboratory values that might indicate peritonitis are a CRP > 75 and white blood cell count > 10.000/mm3, although sensitivity and specificity of these tests are relatively low.[6,57,58] Electrolytes are often disturbed in patients with a bowel obstruction; in particular, low values of potassium are frequently found and need to be corrected. BUN/creatinine needs to be assessed as patients with ASBO are frequently dehydrated which could result in acute kidney injury.

*Imaging studies*

Plain X-rays

The value of plain X-rays complementary to physical examination is limited. In high-grade obstruction, a triad of multiple air-fluid levels, distention of small bowel loops, and absence of gas in the colon are pathognomonic for small bowel obstruction, but overall sensitivity and specificity of plain x-rays is low (sensitivity approximately 70%).[59,60] A large volume

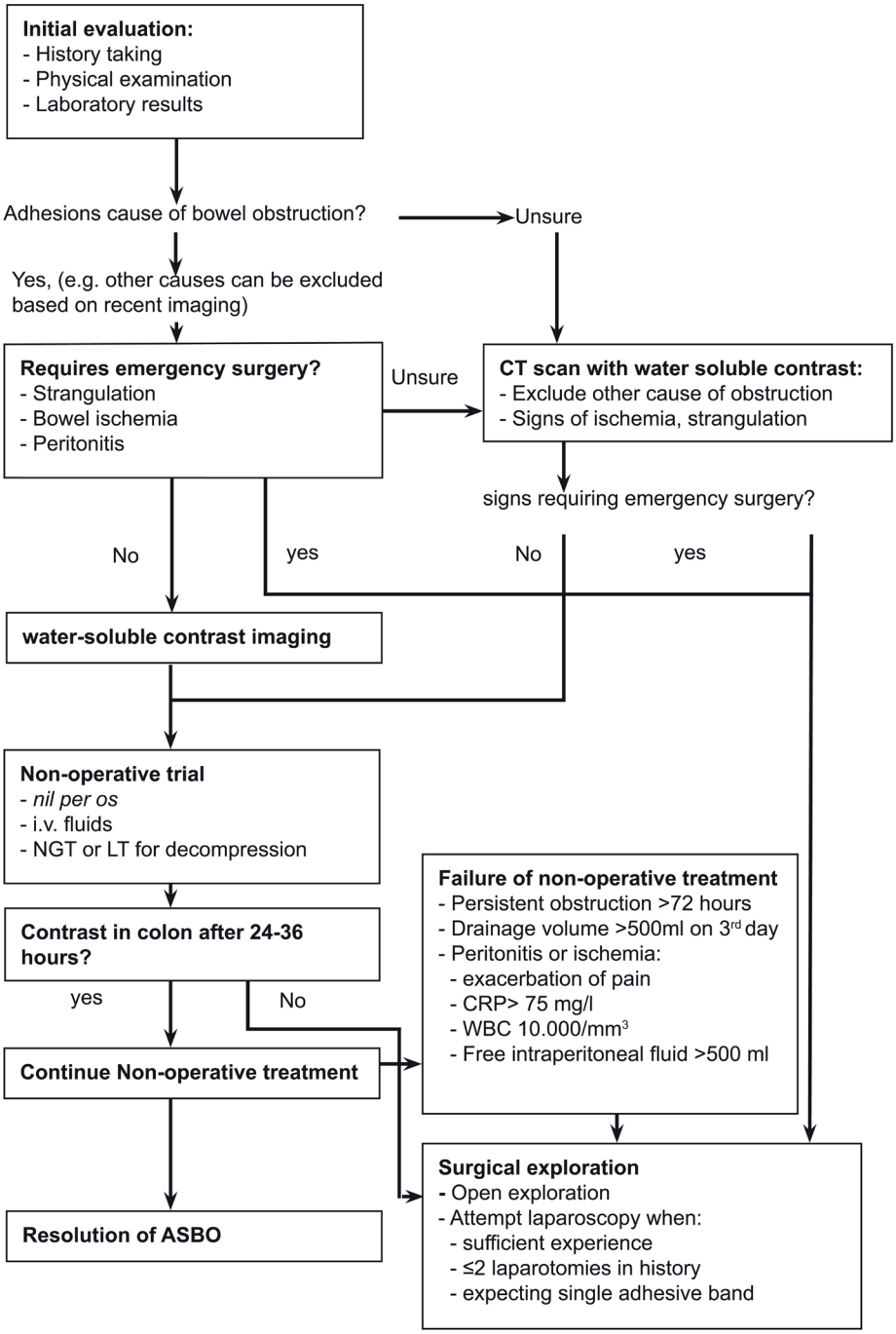



**Figure 2** Algorithm to diagnosis and treatment of ASBO

pneumoperitoneum secondary to bowel perforation in ASBO can also be detected on plain X-rays, preferably by an erect chest X-ray. Plain X-rays, however, do not detect the more early signs of peritonitis or strangulation.[59-61] Furthermore, a plain abdominal X-ray does not provide anatomical information that helps differentiate between the various causes of bowel obstruction.

Water-soluble contrast studies

Several systematic reviews and meta-analyses have established the usefulness of water-soluble contrast agents in the diagnostic work-up of ASBO.[62-64] If the contrast has not reached the colon on an abdominal X-ray taken 24 h following administration of the contrast, this is highly indicative of failure of non-operative management. Multiple studies have shown that the use of water-soluble contrast agents accurately predicts the need for surgery and reduces hospital stay.[62,63] Some authors also suggest that water-soluble contrast studies reduce the need for surgery, which is attributed to an active therapeutic role of the contrast.[62,63]



CT scans

Current helical CT scans not only have good test characteristics for diagnosing small bowel obstruction but also have approximately 90% accuracy in predicting strangulation and the need for urgent surgery.[37,60,65-68] Diagnostic value of CT scan can be enhanced with the use of water-soluble contract. As with water-soluble contrast studies, progress of the contrast can be evaluated by X-ray at 24 h after CT scan.

Although adhesions are not directly visible even on CT scan, a CT scan can differentiate accurately between different causes of bowel obstruction by excluding other causes. The workgroup therefore considers CT scan to be the preferred imaging technique if there is any doubt about the diagnosis of ASBO, and to assess the need for urgent surgery.

A CT scan should help to differentiate between a complete obstruction of the bowel and help facilitate the decision for a trial of non-operative management versus a decision to proceed to surgery. It may also help to define the location of the obstruction (e.g., high in the jejunum or deep in the pelvis). Signs of a closed loop, bowel ischemia, and free fluid are

signs that suggest the need for surgery without delay. In addition, radiological and clinical scores can be used to predict the need for surgery as described above.[37,38]

Ultrasound and MRI

Although the working group considered CT scan to be the preferred technique for diagnosis of ASBO, ultrasound and MRI might be useful in specific situations. Ultrasound is operator dependent but in experienced hands can provide more information than plain X-rays, and is also available in most low income settings. Apart from distension of bowel loops, ultrasound enables detection of free fluid (that might indicate the need for urgent surgery) and assessment of the degree of shock in dehydrated patients.[61,69] Ultrasound can also be of value in situations in which exposure to radiation is undesirable, such as in pregnant patients. In these cases, ultrasound might be complemented with MRI for more anatomical information if the diagnosis of bowel obstruction is confirmed.[70]

Diagnosis: summary

Recommendations can be found in Table 5. In summary, CT scan with oral water-soluble contrast is the preferred technique of imaging in the initial evaluation. Progress of the contrast should be monitored after 24 h of non-operative treatment by X-ray. If the diagnosis of ASBO is certain (e.g., because other causes have been excluded with recent imaging), and there are no signs that immediate surgery might be warranted, only a water-soluble contrast study is considered sufficient. Ultrasound and MRI can be useful in specific situations, such as pregnancy or (in low income countries) when CT scan is unavailable.

*Management*

Initial decision making

Non-operative management should always be tried in patients with adhesive small bowel obstruction, unless there are signs of peritonitis, strangulation, or bowel ischemia.[71] Although the risk of recurrence is slightly lower after operative treatment, this is not a reason to opt for a primary surgical approach. Morbidity from emergency surgical

exploration is high; there is a considerable risk for bowel injury, and surgical treatment may significantly reduce post-operative quality of life.[1,72–74]

Non-operative management

The cornerstone of non-operative management is nil per os and decompression using a naso-gastric tube or long intestinal tube. Non-operative management is effective in approximately 70–90% of patients with ASBO.[1,75,76] There has been some debate in the literature over the use of long intestinal tubes or naso-gastric tubes. In an older trial, no significant difference in failure rates was found between naso-gastric tubes and long intestinal tubes.[77] In a more recent trial, 186 patients were randomized between a newly designed trilumen long tube and a naso-gastric tube. Long tubes seemed more effective in this trial with a failure rate of 10.4% in this group compared with 53.3% in the naso-gastric tube group.[78] Results from this trial should be interpreted with care, because the failure rate of naso-gastric tube compression is much higher than would be expected from other literature. Moreover, a drawback of trilumen tubes is the need for endoscopic placement. Non-operative management should further include fluid resuscitation, correction of electrolyte disturbances, nutritional support, and prevention of aspiration.



Duration of the period in which non-operative management can be tried is subject to debate. Several retrospective series and databases have shown that delays in surgery increase morbidity and mortality.[30,71,79,80] Evidence for the optimal duration of non-operative treatment is absent, but most authors and the panel consider a 72 h period as safe and appropriate.[11,58,76,79,80] Continuing non-operative treatment for more than 72 h in cases with persistent high output from a decompression tube, but no other signs of clinical deterioration, however, remains subject to debate. Common medical complications in patients with small bowel obstruction are dehydration with kidney injury, electrolyte disturbances, malnutrition, and aspiration.

Non-operative management: summary

The panel recommends a trial of non-operative management in all patients with ASBO, unless there are signs of peritonitis, strangulation, or bowel ischemia. Evidence for the

optimal duration of non-operative is absent, but most authors and the panel consider a 72 h period as safe and appropriate. Further recommendations are found in Table 5.

Operative management

Historically, abdominal exploration through laparotomy has been the standard treatment for adhesive small bowel obstruction. In recent years, however, laparoscopic surgery for ASBO has been introduced. The potential benefits of laparoscopy include less extensive adhesion (re)formation, earlier return of bowel movements, reduced post-operative pain, and shorter length of stay.[81–83] In a recent systematic review and meta-analysis of 14 non-randomized studies, laparoscopic adhesiolysis reduced risk of morbidity, in-hospital mortality, and surgical infections.[84] However, there also seems strong selection bias in these series allocating mainly the less severe cases to laparoscopy. In a questionnaire among surgeons, 60% of the respondents reported to have performed laparoscopic adhesiolysis for ASBO in their practice, but half of them in less than 15% of cases.[11]

Although laparoscopy might provide some benefits to some patients for ASBO, surgeons should carefully select candidates for laparoscopic treatment. Laparoscopy in an abdomen with very distended loops of bowel and multiple complex adhesions could increase the risk of severe complications such as enterotomies and delayed diagnosis of perforations.[85,86] Indeed, some authors have reported bowel injury in 6.3 to 26.9% of patients treated with laparoscopic adhesiolysis for ASBO.[87–89] In a recent population-based study, bowel resections were significantly more frequent in laparoscopic surgery. Incidence of bowel resection was 53.5% versus 43.4% in laparoscopic versus open procedures.[90] Farinella et al. reported that predictors for a successful laparoscopic treatment of ASBO are the following: ≤ 2 laparotomies in history, appendectomy as the operation in history, no previous median laparotomy incision, and a single adhesive band.[91] Laparoscopic adhesiolysis also seems more difficult in patients who have previously been treated by radiotherapy.[92]

More compelling evidence on the role of laparoscopy in surgery for ASBO is from an ongoing randomized trial and is still awaited.[93] In this trial, strict inclusion and exclusion criteria have been used to select candidates in whom simple single band adhesions are expected.

Operative management: summary

Laparoscopic surgery has been introduced in recent years and might decrease morbidity in subgroups of patients undergoing surgery for ASBO. The risk of bowel injuries seems higher in laparoscopic surgery for ASBO. Therefore, careful selection of patients for laparoscopic surgery is required. Further recommendations are found in Table 5.

*Special patient groups*

Young patients

The risk of adhesion-related complications is life-long. Although most small bowel obstructions will occur within the first 2 years after surgery, new cases continue to develop many years after the primary operation.[1,30,72,94,95] Also, the risk of requiring a future reoperation for unrelated causes is higher in younger patients.[96] Pediatric patients, who are at the extreme of young age, have a high risk for adhesion-related complications.[1] In a recent cohort of patients who underwent surgery at a pediatric age, the incidence of adhesive small bowel obstruction was 12.6% after a median follow-up of 14.7 years.[29]

Young patients therefore might have the highest lifetime benefit from adhesion prevention.[49] No trials with adhesion barriers have been performed in pediatric surgery, but a recent cohort study in pediatric patients showed a significant reduction in ASBO with the use of a hyaluronate carboxymethylcellulose adhesion barrier.[97] After a follow-up of 24 months, 2.0% of pediatric patients operated with adhesion barrier versus 4.5% of patients operated on without adhesion barrier developed ASBO.

Elderly patients

In elderly patients, quality of life considerations are extremely important in decision making. Patients with a high frailty index have a prolonged recovery after a surgical procedure and may not be able to return to their previous functional state and quality of life.[98,99]

The principles of treatment for adhesive small bowel obstruction might interfere with comorbidities and medication in the elderly patients. There is a marked paucity of research

**Table 5** Overview of conclusions and recommendations

| | |
|---|---|
| Level A | Adhesive small bowel obstruction is a leading cause of morbidity, deaths, and healthcare expenditures in emergency surgery.<br>*A2 Scott 2016; NELA project team 2016* |
| Level B | Adhesive small bowel obstruction causes high morbidity, with average hospital stay of 8 days and 3% in-hospital mortality per episode. Recurrence of adhesive small bowel obstruction is high. Risk for adhesive small bowel obstruction may be somewhat lower after laparoscopic compared to open colorectal surgery, but that results could not be confirmed in randomized trials.<br>*A2 ten Broek, 2013; Yamada 2016; B Krielen 2016; Foster 2006* |
| Level IB | Laparoscopic surgery reduces adhesion formation and might reduce subsequent incidence of ASBO.<br>*B Lundorff 1992; ten Broek 2013; Yamada 2016* |
| Level IA | Hyaluronate carboxymethylcellulose reduces adhesion formation and the risk of subsequent reoperations of adhesive SBO. Use of this barrier seems cost-effective in open colorectal surgery.<br>*A1 ten Broek 2014*<br>*A2 Fazio 2006; Park 2009; Kusunoki 205* |
| Level IIC | In the absence of signs that require emergent surgical exploration (i.e. peritonitis, strangulation, or bowel ischemia), non- operative management is the treatment strategy of choice.<br>*C Fevang 2002; Fevang 2004; Ten Broek 2013; Jeppesen 2016* |
| Level IIB | A trial of non- operative management can be continued safely for 72 hours.<br>*B Keenan 2014; Sakakibara 2007* |
| Level IID | Initial evaluation should be complemented with assessment of nutritional status and laboratory tests evaluating at least blood count, lactate, electrolytes, and BUN/ Creat<br>*D Expert opinion* |

| | |
|---|---|
| Level IIC | Plain x-rays have only limited value in the work-up of patients with small bowel obstruction and are not recommended.<br>*B Maglinte 1996* |
| Level IB | Optimal diagnostic work-up should include CT-scan in the assessment and water soluble oral contrast. In the absence of the need to perform immediate surgery, a follow-up abdominal x-ray should be made after 24 hours. If the contrast has reach the colon this is indicative for resolution of the bowel obstruction.<br>*A2 Ceresoli 2016; Branco 2010; Abbas 2005*<br>*B Goussous 2013*; *Zielinski 2011; Zielinski 2010; Daneshmat 1999; Makita 1999; Zalcman 2000* |
| Level IIC | Long trilumen naso-intestinal tubes are more efficacious than naso-gastric tubes in non-operative management, but require endoscopic placement.<br>*A2 Chen2012* |
| Level IIC | Laparoscopic adhesiolyis might reduce morbidity in selected cases of ASBO that require surgery. Results of a randomized trial are awaited.<br>*B Sajid 2016; Farinella 2009; Sallinen 2014* |
| Level IIB | Adhesion barriers reduce the risk of recurrence for ASBO following operative treatment.<br>*A2 Catena 2012* |
| Level IIC | Younger patients, and pediatric patients in particular, have higher life-time risk of developing adhesion- related complications and might therefore benefit most from adhesion prevention.<br>*A1 ten Broek 2013; A2 Strik 2016; B Fredriksson 2016* |
| Level C | More research is needed to the impact of comorbidities in elderly patients on optimal management of adhesive small bowel obstruction. Patients with diabetes might require more early operative intervention.<br>*B Karamanos 2016* |

on the consequences of stopping or withholding oral medications when a patient is put on nil per os for non-operative treatment of small bowel obstruction. A recent cohort showed that patients with diabetes might require earlier intervention although the level of evidence is rather low. Patients with diabetes were shown to suffer from a 7.5% incidence of acute kidney injury and 4.8% incidence of myocardial infarction if the operation was delayed more than 24 h.[100] The incidence of these complications was significantly higher when compared to diabetic patients that were operated within 24 h and non-diabetic patients with delayed operation.

Pregnancy

Small bowel obstruction in pregnancy is very rare but represents an important clinical challenge with significant risk of fetal loss. In a recent review, 46 cases of bowel obstruction during pregnancy were found in literature from case series and case reports.[101] Approximately half of cases were attributed to adhesions, most commonly from previous abdominal operations. Imaging studies performed to diagnose SBO in the case reports included ultrasound in ten cases (83%), abdominal X- ray in four patients (33%), MRI in four patients (33%), and a CT scan in three patients (25%). Strikingly, the failure rate of non-operative treatment in pregnant patients with ASBO was high. A total of 23 cases with ASBO were reported, in 17 of whom initial management was by a non-operative trial. Non-operative treatment failed in 16 cases (94%). Risk of fetal loss was 17% (n = 8) and risk of maternal death 2% (n = 1).

**Conclusions**

The conclusions and recommendations of this guideline have been summarized in Table 5. ASBO is a common surgical emergency, causing high morbidity and even some mortality. Surgeons should be aware that the adhesions causing such bowel obstructions are typically the footprints of previous abdominal surgical procedures or disease. Part of the adhesion formation can be prevented by application of minimal invasive surgical techniques and the use of adhesion barriers. Most cases of ASBO can be treated non-operatively. If operative treatment is required, a laparoscopic approach might be beneficial for simple cases. However, there is a considerable risk for conversion to an open laparotomy and care needs to be taken not to make bowel injury.

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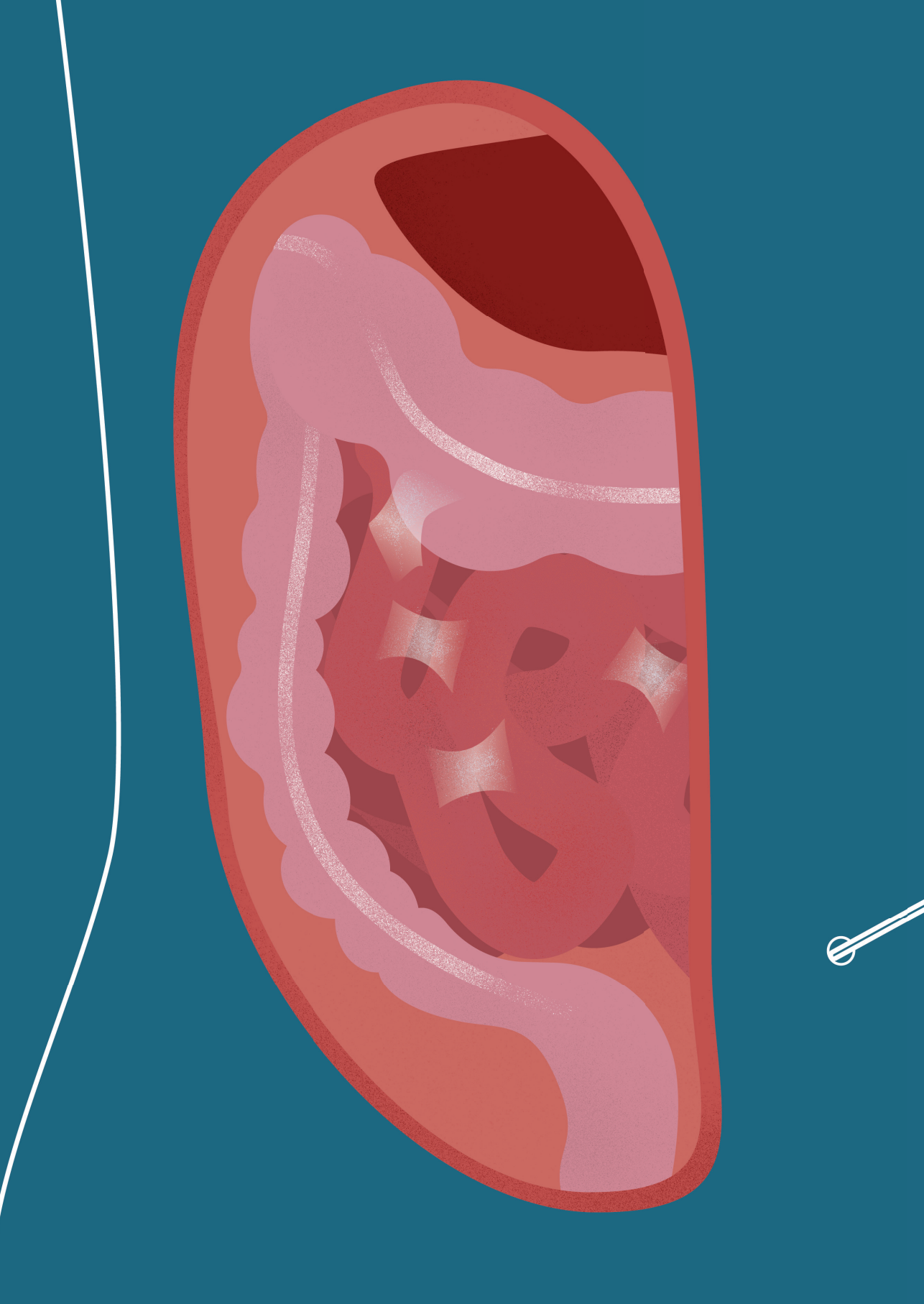
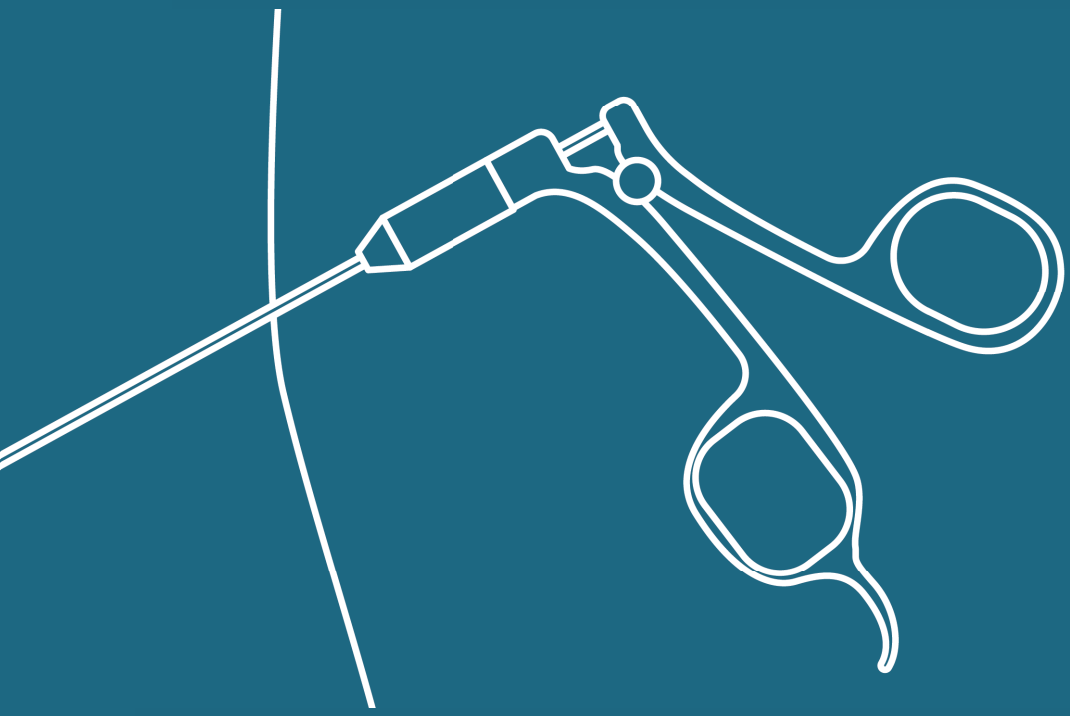


# 6

# Laparoscopic versus open approach for adhesive small bowel obstruction, a systematic review and meta-analysis of short term outcomes



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**Abstract**

*Background*

Adhesive small bowel obstruction (ASBO) is one of the most frequent causes of emergency hospital admissions and surgical treatment. Current surgical treatment of ASBO consists of open adhesiolysis. With laparoscopic procedures rising, the question arises if laparoscopy for ASBO is safe and results in better patient outcomes. Although adhesiolysis was among the first surgical procedures to be approached laparoscopically, uncertainty remains about its potential advantages over open surgery. Therefore, we performed a systematic review and meta-analysis on the benefits and harms of laparoscopic surgery for ASBO.

*Methods*

A systematic literature review was conducted for articles published up to May 2019. Two reviewers screened all articles and did the quality assessment. Consecutively a meta-analysis was performed. To reduce selection bias, only matched studies were used in our primary analyses. All other studies were used in a sensitivity analyses. All the outcomes were measured within the 30th postoperative day. Core outcome parameters were postoperative mortality, iatrogenic bowel perforations, length of postoperative stay [days], severe postoperative complications, and early readmissions. Secondary outcomes were operative time [min], missed iatrogenic bowel perforations, time to flatus [days], and early unplanned reoperations.

*Results*

In our meta-analysis, 14 studies (participants = 37.007) were included: 1 randomized controlled trial, 2 matched studies, and 11 unmatched studies. Results of our primary analyses show no significant differences in core outcome parameters (postoperative mortality, iatrogenic bowel perforations, length of postoperative stay, severe postoperative complications, early readmissions). In sensitivity analyses, laparoscopic surgery favored open adhesiolysis in postoperative mortality (relative risk [RR], 0.36; 95% CI, 0.29 to 0.45), length of postoperative hospital stay (mean difference [MD], −4.19; 95% CI, −4.43 to −3.95), operative time (MD, −18.19; 95%CI, −20.98 to −15.40), time to flatus (MD, −0.98; 95% CI,

−1.28 to −0.68), severe postoperative complications (RR, 0.51; 95% CI, 0.46 to 0.56) and early unplanned reoperations (RR, 0.82; 95% CI, 0.70 to 0.96).

*Conclusion*

Results of this systematic review indicate that laparoscopic surgery for ASBO is safe and feasible. Laparoscopic surgery is not associated with better or worse postoperative outcomes compared with open adhesiolysis. Future research should focus on the correct selection of those patients who are suitable for laparoscopic approach and may benefit from this approach.

**Introduction**

Small bowel obstruction (SBO) is one of the leading causes of an emergency admission to a general surgical ward and one of the most frequent indications for emergent abdominal operations worldwide.[1,2] Adhesions are the most common etiology for SBO in developed world countries and account for approximately 60% of all episodes.[3–5] The incidence of adhesive SBO (ASBO) is related to the extent of peritoneal injury in patients who underwent surgery, or with a history of inflammatory bowel disease.[6] Hospital stay for an episode of ASBO can easily be prolonged for over 1 week, regardless from nonoperative or operative management.[7,8] Recurrence rates for an episode of ASBO are high,[9] operative management of a first episode of ASBO might reduce the risk of readmission for ASBO.[10] Operative management of ASBO usually consists of an exploratory laparotomy with adhesiolysis. With the rise of laparoscopic surgery, and its many benefits, laparoscopic adhesiolysis has been suggested as a new surgical approach to ASBO. Potential benefits of laparoscopic adhesiolysis include faster recovery, less pain, and fewer recurrences of adhesions.[11] The first laparoscopic adhesiolysis for ASBO was performed in 1972 by Mouret.[12] Since several papers have published favorable results of the laparoscopic approach. Implementation of laparoscopic surgery for ASBO, however, is slow, and there is concern for an increased risk of iatrogenic bowel injury.[13] Unfortunately, evidence supporting laparoscopy over open surgery in reducing the risk for ASBO recurrence is not strong.[14]

With the aim to assess feasibility, safety, and efficacy of laparoscopic adhesiolysis, we conducted a systematic review in 2009, according to the recommendations of The Cochrane Collaboration and the Cochrane Colorectal Group.[15] Search results included no randomized controlled trials (RCTs) or prospective observational studies which compared laparoscopy with open surgery for patients with ASBO.[16]

Nowadays, we have performed an updated systematic review and meta-analysis, analyzing the available evidence from the literature on the benefits and harms of laparoscopic surgery for ASBO.

## Material and methods

We performed a systematic review of literature up to 20 May 2019 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] The protocol of this systematic review and meta-analysis has been registered on PROSPERO CRD42018107087 (http://www.crd.york.ac.uk/prospero). This systematic review included RCTs, matched studies, and unmatched studies, irrespective of their publication status or language. General population (children and adults), irrespective of race, sex, health status, or geographical location, who have undergone full laparoscopic or laparoscopy-assisted versus open adhesiolysis for ASBO were included in this review.

*Types of outcome measures*

All the outcomes were measured within the 30th postoperative day. Primary outcome were the results of comparison of laparoscopic and open surgery for ASBO in RCTs and matched cohort studies on core clinical outcomes. Five core clinical outcome parameters were defined: postoperative mortality, iatrogenic bowel perforation, severe postoperative complications, length of postoperative hospital stay (LOS) [days] and early unplanned readmissions (within 30 days of discharge). Severe postoperative complications were classified as Clavien-Dindo III–IV.[18] Secondary outcome measures were operative time [minutes], missed iatrogenic bowel injuries, unplanned reoperations (within 30 days of discharge), and time to flatus [days]. A radar chart was constructed to visualize differences in core clinical outcome parameters.

*Literature search strategy*

A systematic literature search was performed in PubMed, Scopus andWeb of Science, for studies reporting data on laparoscopic management of ASBO, published between 1980 and 2019. The search was performed by entering the following keywords: (“laparoscopic adhesiolysis” OR “laparoscopic lysis” OR “laparoscopic management”) “AND (“small bowel obstruction” OR “adhesive bowel obstruction”). Two independent reviewers (RC, NV) individually assessed all titles and abstracts focusing on laparoscopic adhesiolysis for ASBO. Disagreement was solved through discussion. In case of persistent disagreement, the study

was discussed with a third reviewer. Successively the full-text of relevant studies were obtained and evaluated. After inclusion, data from each study were independently extracted by two reviewers. If necessary, we contacted the corresponding author of the study to obtain additional research data.

*Assessment of risk of bias in included studies*

The risk of bias of the included studies was independently assessed by two independent reviewers (RC, NV). To evaluate the methodological quality of the included studies the Cochrane "risk of bias" assessment tool for RCTs[19,20] and the methodological index for nonrandomized studies (MINORS) were used.[21] In RCTs, the risk of bias was considered high if a high risk was scored in one or more of the five key domains. In nonrandomized studies, the risk of bias was considered high if the MINORS score resulted in greater than 20 points, or groups were not adequately matched (see below). Analysis of publication bias was performed using a funnel plot.

*Matching methods were assessed in all included studies.*

For a study to be included in the matched study group, matching should have been based on relevant surgical items. The definition of relevant surgical items for matching results from discussion between the authors and reflect selection criteria for patients in RCTs. Consensus was reached that we considered matching of sufficient quality to consider a study as low risk of bias, if matching factors comprised at least the following three domains: (1) expected or observed extend and type of adhesions (e.g., number of previous abdominal operations performed laparoscopic or open, type of adhesions observed [single band/dense adhesions]); (2) descriptors indicating critical illness (e.g. suspected perforation before surgery, sepsis, suspected strangulation); (3) medical history (e.g., American Society of Anesthesiologists [ASA] status, comorbidity). If studies were not matched on all three domains, we considered them high risk of bias, and the study was not used in the primary analyses of the primary and secondary outcome measures for this review. Thus, these studies were used in the unmatched analysis.

*Analysis*

Core clinical outcome parameters and secondary outcome parameters were separately analyzed for RCTs and matched studies and for unmatched studies. All matched studies were included in the analysis of primary and secondary outcome measures. Unmatched studies were included only in sensitivity analyses. We used the Mantel-Haenszel method for dichotomous data, presented as relative risks (RR) with 95% confidence intervals (CIs). We used the inverse variance method to pool continuous data; results are presented as mean difference with 95% CIs. Analyses were based on "intention-to-treat," that is, all patients in whom laparoscopic surgery was converted to open surgery were analyzed in the laparoscopic group. The I2 test was used for heterogeneity assessment. A value exceeding 50% was significant of heterogeneity. In the absence of statistical heterogeneity, we used a fixed-effect model; otherwise, we used a random-effects model. The data analysis was performed using the meta-analysis software Review Manager (RevMan) v 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2018).

*Sensitivity analysis*

As a sensitivity analysis, we performed analysis of all studies, including the unmatched cohorts. Outcome measures were compared between the matched studies and all studies (including the unmatched studies).



**Results**

We retrieved 1.927 records with our search strategy, 973 records were excluded because they were duplicated. Subsequently, 954 titles and abstracts were evaluated, 930 abstracts were excluded because they did not meet inclusion criteria. Full text was evaluated in 24 studies: 14 studies included[22–35] and 10 excluded[36–45] (Fig. 1).

The characteristics of excluded studies and the reasons for the exclusion are reported in Supplemental Digital Content 1, Table 1.

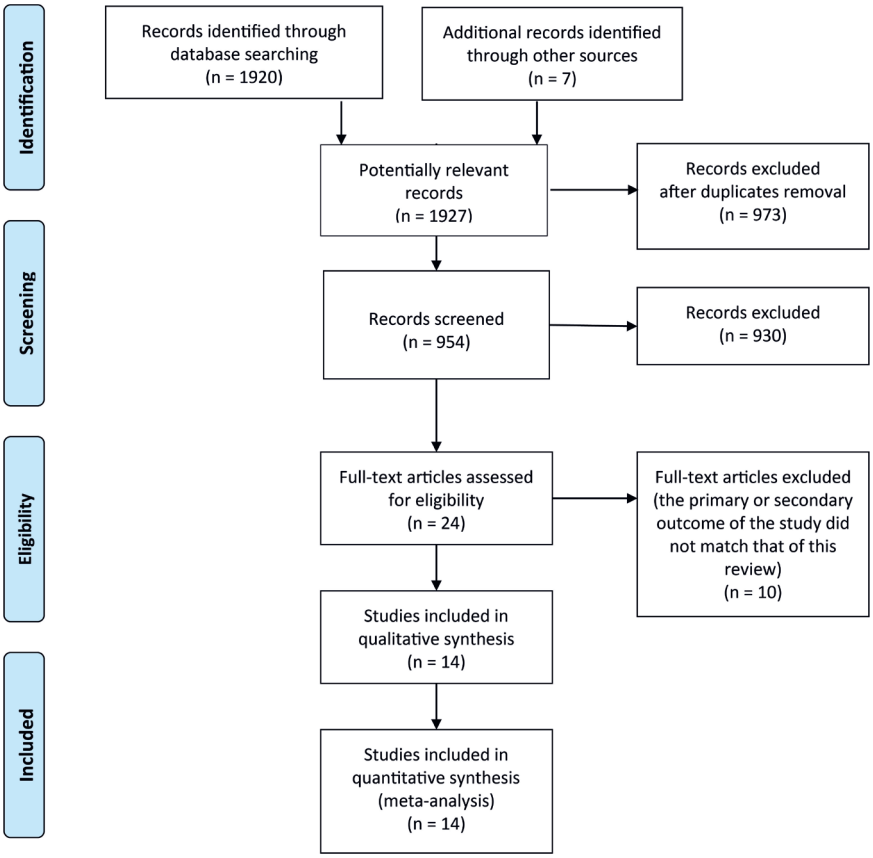



**Figure 1** PRISMA flow diagram, PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

*Characteristics of the studies included*

In 14 studies 37.007 patients were enrolled, including 1 RCT (n = 100).[22–35] After assessment of matching methods, 2 studies (n = 154) were classified as matched studies, and 11 studies were classified as unmatched studies (n = 36.753) (Supplemental Digital Content 2, Table 2). The RCT, laparoscopic versus open adhesiolysis for adhesive small bowel obstruction (LASSO) trial, was performed in two countries (Finland and Italy) and enrolled 100 patients between 2013 and 2018.[22] The duration of the enrolment of the participants reported, ranged between 1 and 11 years.

*Methods of matching*

Matching in the study of Hackenberg et al. was performed using propensity score-matching based on items in all three matching categories. Surgical aspects included: ASA classification, number of previous abdominal operations, number of previous conservatively managed ASBO episodes, duration of symptoms, suspected bowel strangulation, hemodynamically unstable. Based on these items, there was a low risk of selection bias.

Yao et al. matched on items in all three categories using propensity score matching, including: Systemic Inflammatory Response Syndrome (SIRS) (at presentation), ASA classification, comorbidities, type of adhesions (isolated band, simple, dense), time to operation, number of previous abdominal operations, comorbidities, and maximum bowel diameter on CT. This study was marked as a low risk of selection bias.

Some other studies attempted matching but did not match on all three predetermined domains.

*Quality assessment of the studies included*

Intention to treat design was applied in 10 studies (Supplemental Digital Content 2, Table 2). According to the author's judgment, the assessment of the RCT showed a “low risk of bias” in the greatest number of analyzed items (random sequence generation, selection bias, allocation concealment, selection bias), whereas a high risk of bias was reported for blinding of participants and personnel (performance bias). The mean score of the methodological assessment of the matched studies was 20 (moderate risk) (Supplemental Digital Content 3, Table 3). Mean score for unmatched studies was 18 (high risk) (Supplemental Digital Content 3, Table 3). A summary of the main findings per study is provided in Supplemental Digital Content 4, Table 4.

*Core clinical outcomes*

Postoperative 30-day mortality

Mortality was reported in the RCT, and all two matched studies. There was no significant difference in mortality between the laparoscopic (1.6%, 2/128) and open adhesiolysis cohort (2.4%, 3/126) (RR, 0.70; 95% CI, 0.14 to 3.51; I2 = 0%; Fig. 2A).

Iatrogenic bowel perforation

This parameter was reported in the RCT and one matched study. There was no significant difference in iatrogenic bowel perforations between the laparoscopic (10.5%, 8/76) and open adhesiolysis cohort (4.1%, 3/74) (RR, 2.61; 95% CI, 0.72 to 9.42; I2 = 0%; Fig. 2B).

Length of postoperative hospital stay (days)

The LOS was only reported in the RCT. There was no significant difference in LOS between the laparoscopic and open adhesiolysis cohort (MD, −1.30; 95% CI, −1.30 to 0.74, I2 = not applicable [NA]; Fig. 2C).

Severe postoperative complications

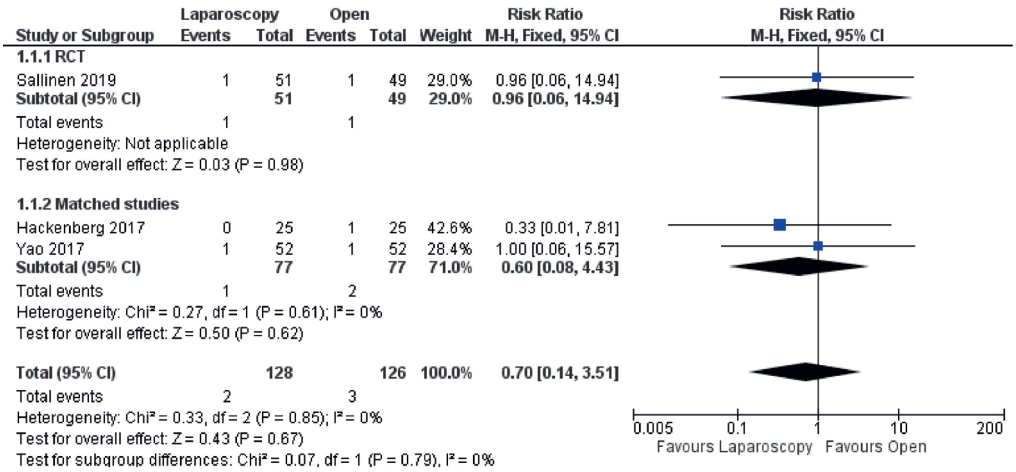
The RCT and one matched study reported this outcome parameter. There was no significant difference in the incidence of severe postoperative complications between the laparoscopic (5.3%, 4/76) and open adhesiolysis cohort (4.1%, 3/74) (RR, 1.28; 95% CI, 0.30 to 5.43; I2 = NA; Fig. 2D).

Early readmissions (within 30 days of discharge)

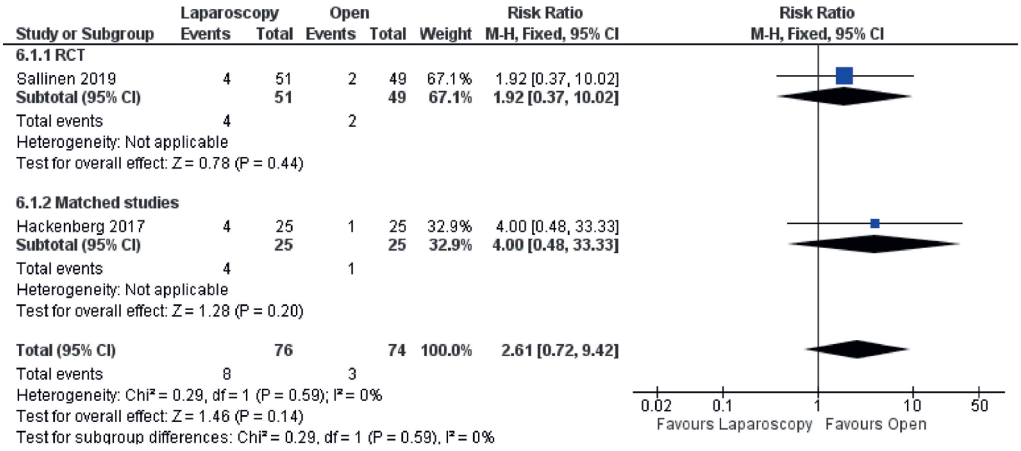
Only the RCT reported this outcome. There was no significant difference in the incidence of early unplanned readmissions between the laparoscopic (5.9%, 3/51) and open adhesiolysis cohort (2.0%, 1/49) (RR, 2.88; 95% CI, 0.31 to 26.78; I2 = NA; Fig. 2E).

A summary of core clinical outcome parameters is visualized in Figure 3.

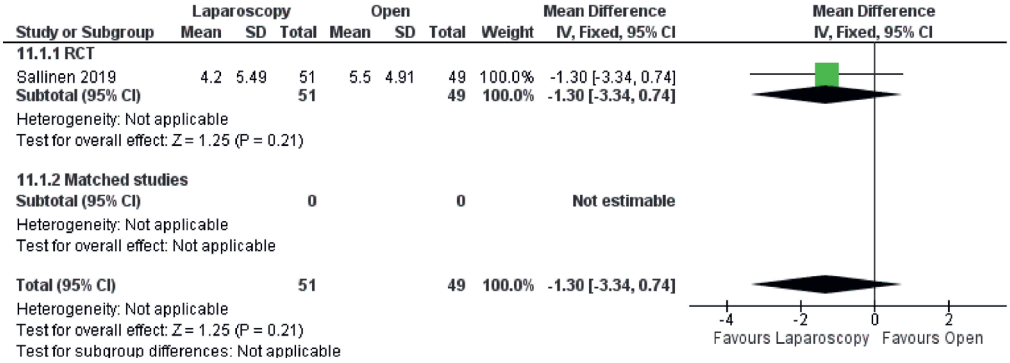
A. Postoperative 30-day mortatlity



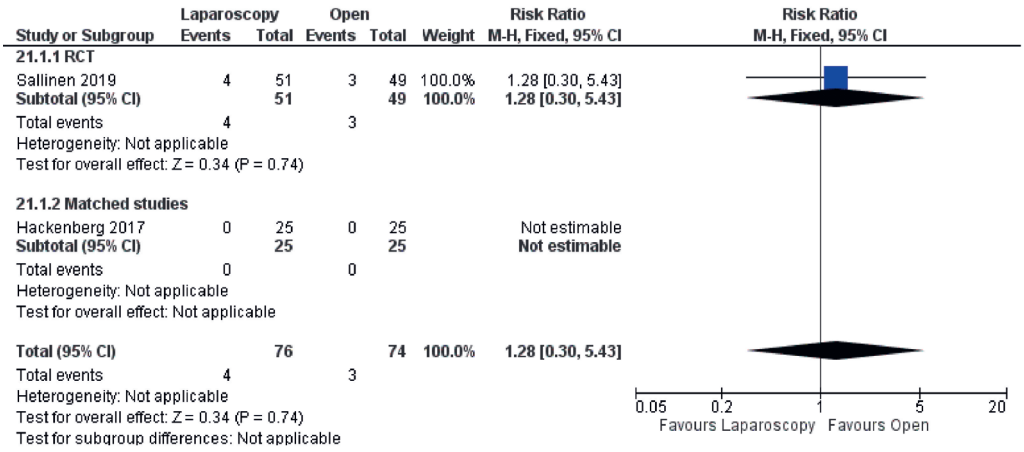

B. Iatogenic bowel perforations




C. Length of postoperative stay



D. Severe post-operative complications




E. Early readmissions

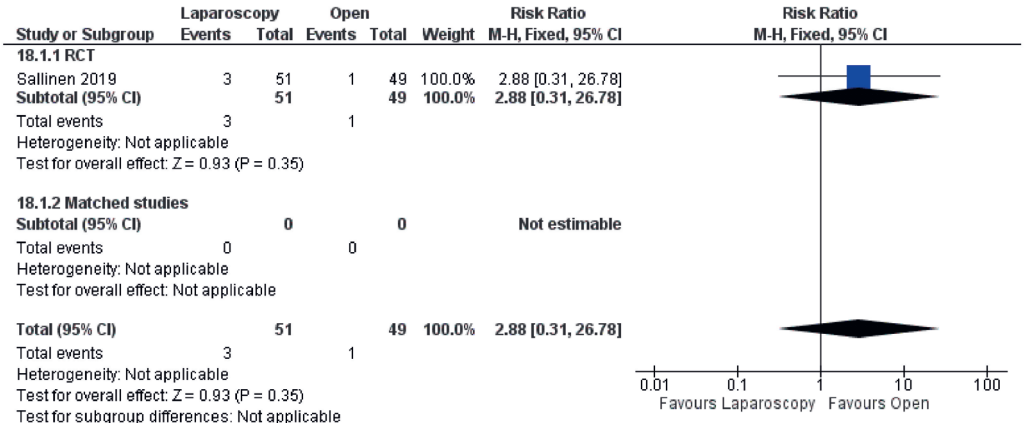



**Figure 2** Forest plot core clinical outcomes

*Secondary outcomes*

Operative time (min)

Operative time was not reported in the RCT or any of the matched studies.

Missed iatrogenic bowel perforation

The RCT and one matched study presented this outcome. There was no significant difference in the incidence of missed iatrogenic bowel perforations between the laparoscopic (1.3%, 1/76) and open adhesiolysis cohort (0%, 0/74) (RR, 2.88; 95% CI, 0.12 to 69.16; I2 = NA) (Supplemental Digital Content 5, Figure 1).

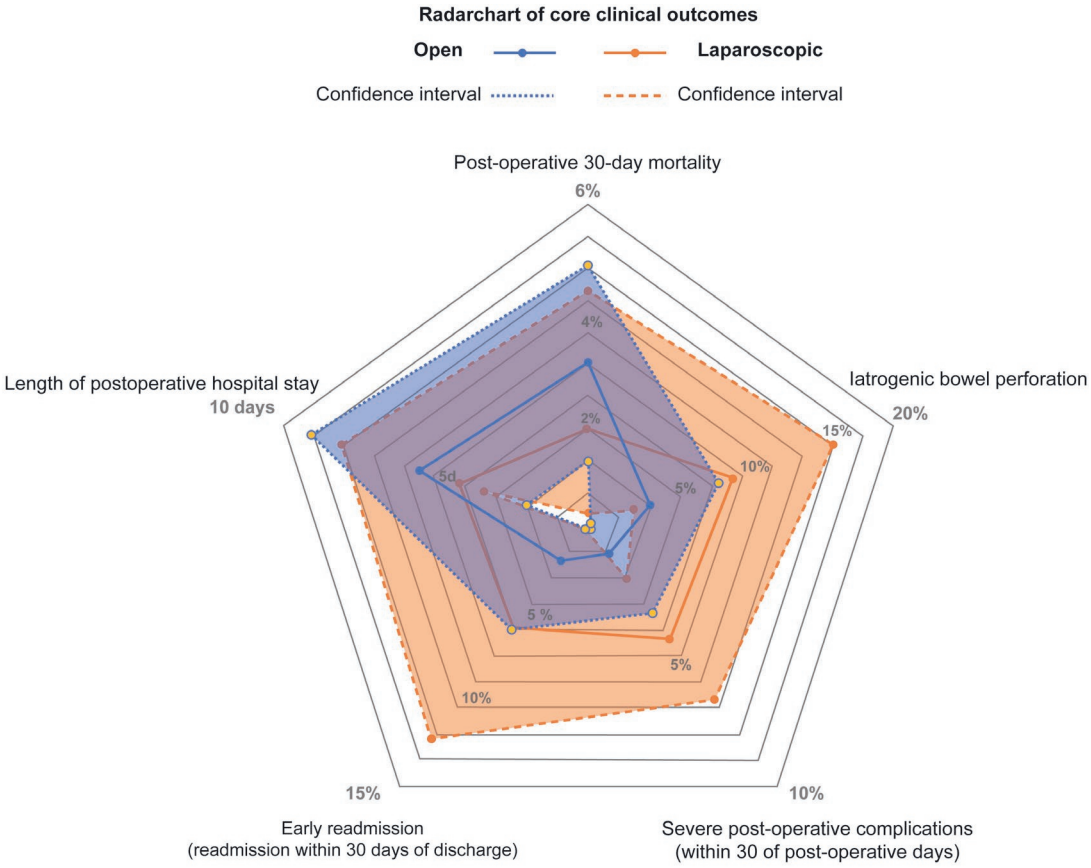



**Figure 3** Radar chart core clinical outcome

Time to flatus (days)

Time to flatus was only reported by Yao et al. Patients in the laparoscopic cohort had a decrease in time to flatus compared with the open adhesiolysis cohort (MD, −1.00; 95% CI, −1.58 to −0.42; I2 = NA) (Supplemental Digital Content 6, Figure 2).

Early unplanned reoperation (30 postoperative days)

The incidence of unplanned reoperations was only reported by the RCT. There was no significant difference in the incidence of early unplanned reoperations between the laparoscopic (2.0%, 1/51) and open adhesiolysis cohort (0%, 0/49) (RR, 2.88; 95% CI, 0.12 to 69.16; I2 = NA) (Supplemental Digital Content 7, Figure 3).

*Sensitivity analyses*

All studies included (including unmatched studies)

In sensitivity analyses (Supplemental Digital Content 8, Figs. 4–12), laparoscopic surgery favored open adhesiolysis in postoperative mortality (RR, 0.36; 95% CI, 0.29 to 0.45; I2 = 0%), LOS (MD, −4.19; 95% CI, −4.43 to −3.95; I2 = 97%), operative time (MD, −18.19; 95% CI, −20.98 to −15.40; I2 = 65%), time to flatus (MD, −0.98; 95% CI, −1.28 to −0.68; I2 = 0%), severe postoperative complications (RR, 0.51; 95% CI, 0.46 to 0.56; I2 = 55%), and early unplanned reoperations (RR, 0.82; 95% CI, 0.70 to 0.96; I2 = 0%). There were no differences in other parameters.

**Discussion**

Fourteen studies were identified that met the criteria to answer our primary or secondary research questions. Results of this systematic review and meta-analysis showed no evidence of superiority for one technique over the other on core clinical outcomes. In sensitivity analysis laparoscopic adhesiolysis for ASBO was associated with a decrease in 30-day mortality, LOS, operative time, time to flatus, risk of severe postoperative complications, and early unplanned reoperations. However, given the methodological

limitations of the unmatched studies, these results might be attributable to patient selection.

Laparoscopic surgery for ASBO theoretically offers a number of potential benefits over open surgery (e.g., shorter length of stay, reduction in adhesion reformation), the choice of the best surgical approach in a clinical setting should be made according to many factors. Situations with contraindications for pneumoperitoneum, such as hemodynamic instability, sever bowel distention, or cardiopulmonary impairment, will require an open approach.[36,46] Other factors possibly influencing the selection of surgical approach are: laparoscopic skills of the surgeon and availability of laparoscopic equipment and instruments. Eligibility criteria for a laparoscopic approach to ASBO are: the absence of peritonitis or severe intra-abdominal sepsis, less than severe distension of the bowel on radiological imaging, anticipated single band or limited extent of adhesions, and surgical skills.[37] As reported in most recent guidelines on the management of ASBO, open surgery is indicated for strangulating ASBO or in case of ischemic bowel loops, while laparoscopic approach is most suitable for selected patients presenting at their first episode and with an anticipated single band detected at preoperative radiological imaging.[5,9]

*Strengths and limitations*

The major strengths of this review are the systematic approach and the inclusion of data from the first randomized trial comparing laparoscopic with open adhesiolysis for ASBO. We thoroughly screened all included articles for matching methods. Only studies that were matched on relevant surgical items were included in the primary analysis, all other studies were used in the sensitivity analysis. Unmatched studies were not used in the primary analysis to reduce the risk of selection bias. Critically ill patients presenting with ASBO are less likely to undergo laparoscopic procedures for many reasons, including the inability to tolerate pneumoperitoneum and are more prone to postoperative complications. For this reason, outcome parameters are likely to favor the laparoscopic surgery group by selection. Sensitivity analyses indeed showed a favorable effect of laparoscopic surgery for ASBO on some of the outcome parameters when unmatched studies were considered.

Potential limitations of this study should be also discussed. Data on severity of adhesions and preoperative findings were not available in all the included studies, making it more difficult to define criteria for selection of patients for laparoscopy. We included only studies in the matched group if an attempt was made to match for the expected or observed extend and type of adhesions (e.g., number of previous abdominal operations performed laparoscopic or open, type of adhesions observed [single band/dense adhesions]). Due to strict selection criteria meta-analysis of some outcomes was based only on one study. These results of the meta-analysis are, therefore, somewhat less reliable. Core clinical outcomes that were only based on only one study were LOS and early readmissions. These parameters were only reported in the LASSO trial.[22] The LASSO trial was powered on length of hospital stay. In their analysis of the geometric means a significant difference was found, although this was not confirmed in our analysis using inverse variance for continues outcomes. The difference was also smaller than accounted for in the sample size calculation of the LASSO trial (1.3 days vs 2.5 shorter hospital stay). A potential beneficial effect of laparoscopy on LOS therefore still needs to be confirmed in future studies that are well matched and powered. Timing of surgery for ASBO also remains a controversial issue; within the included studies there was heterogeneity regarding the timing of surgery. In a recent update of the Bologna guidelines and a Delphi consensus study, for patients not requiring emergent surgical exploration, a trial of nonoperative management can be continued safely as far as for 72 hours.[9,38] When surgery is performed after more than 72 hours of conservative trial, an increase in mortality is observed.[9,39]

A potential limitation of our study is the intention to treat design, therefore, not considering laparoscopic conversions to open surgery. Several studies did not report the causes and outcomes for conversion,[22,26,28–30,32,34,35] or they did not report conversion rates at all. The matched studies had an accurate description of standardized surgical techniques used in the laparoscopic group. Nevertheless, technical biases might occur because laparoscopic surgery for ASBO is a highly complex procedure and results depend on the experience of the surgeon and also the characteristics and localization of the adhesions which requires a tailored surgical approach and a standardized technique. The choice of the surgical approach for ASBO depends on many factors, some of which could be controlled for by

matching in nonrandomized studies. Examples, however, of factors that are difficult to control for in nonrandomized studies include the laparoscopic skills of the surgeon, experience of the full operative team, and the impact of performing surgery at night hours.

There is no broad accepted outcome for restore of bowel function. Many of the included studies use a wide variety of outcome parameters to predict restore of bowel function. Recently, a study was started to develop a core outcome set for gastrointestinal recovery in the context of postoperative ileus and small bowel obstruction.[40] Since, to date, there is no consensus on a single parameter for restore of bowel function, we designed a set of key clinical outcome parameters as primary endpoint for this study. Radar charts are increasingly used in recent years to compare the total value (and sometimes costs) of different interventions, as opposed to comparison on a single outcome parameter.[41]

*Comparison to other literature*

Over the past decades, laparoscopic surgery became the standard of care in several fields of elective surgery. A retrospective study which included over 13.000 patients from the American College of Surgeons prospective National Surgical Quality Improvement Program data set reported a significant increase of application of laparoscopy from 17% in 2006 to 29% in 2013.[42] Grafen et al.[43] found that patients who underwent successful laparoscopic adhesiolysis for ASBO had fewer prior operations and were younger with a lower ASA score, had shorter operative time and postoperative length of stay compared with patients who underwent open or converted adhesiolysis for ASBO. A recent systematic review which included 18 comparative nonrandomized studies ranging from 1990 to 2017 reported that the ASA score of patients who underwent laparoscopic adhesiolysis was significantly lower compared with the open group.[44]

Unlike the results of a recent review, where iatrogenic bowel injury is less frequent in laparoscopic surgery,[44] our review showed no significant difference in the risk of iatrogenic bowel injury in open or laparoscopic adhesiolysis. Moreover, there was no significant difference in missed bowel injuries. Previous studies showed a higher risk of missed bowel injures in the presence of distended bowel and multiple complex adhesions[45,47] and during emergency surgical exploration.[48]

A review published in 2012 concluded that laparoscopy can significantly reduce the duration of postoperative ileus, as well as the incidence of pulmonary complications with no statistically significant reduction of intraoperative bowel injuries rates and overall mortality.[49] In our review, laparoscopic surgery was not associated with a reduction of time to flatus. More recently, another review of 14 nonrandomized studies showed that laparoscopic adhesiolysis can reduce risk of morbidity, in-hospital mortality, and surgical infections.[50] In our primary analyses, we found no difference in postoperative mortality or postoperative complications; however, in sensitivity analysis, laparoscopic surgery might be associated with a decrease in postoperative mortality (RR, 0.36; 95% CI, 0.29 to 0.45), and severe postoperative complications (RR, 0.51; 95% CI, 0.46 to 0.56).

**Conclusion**

The present systematic review showed that laparoscopic surgery for ASBO is feasible, as it is associated with similar adverse events rates compared with open surgery. Nevertheless, we found no evidence for superiority of one technique over the other. Future research should focus on the correct selection criteria to identify which patients are suitable for a laparoscopic approach and may benefit from this approach.

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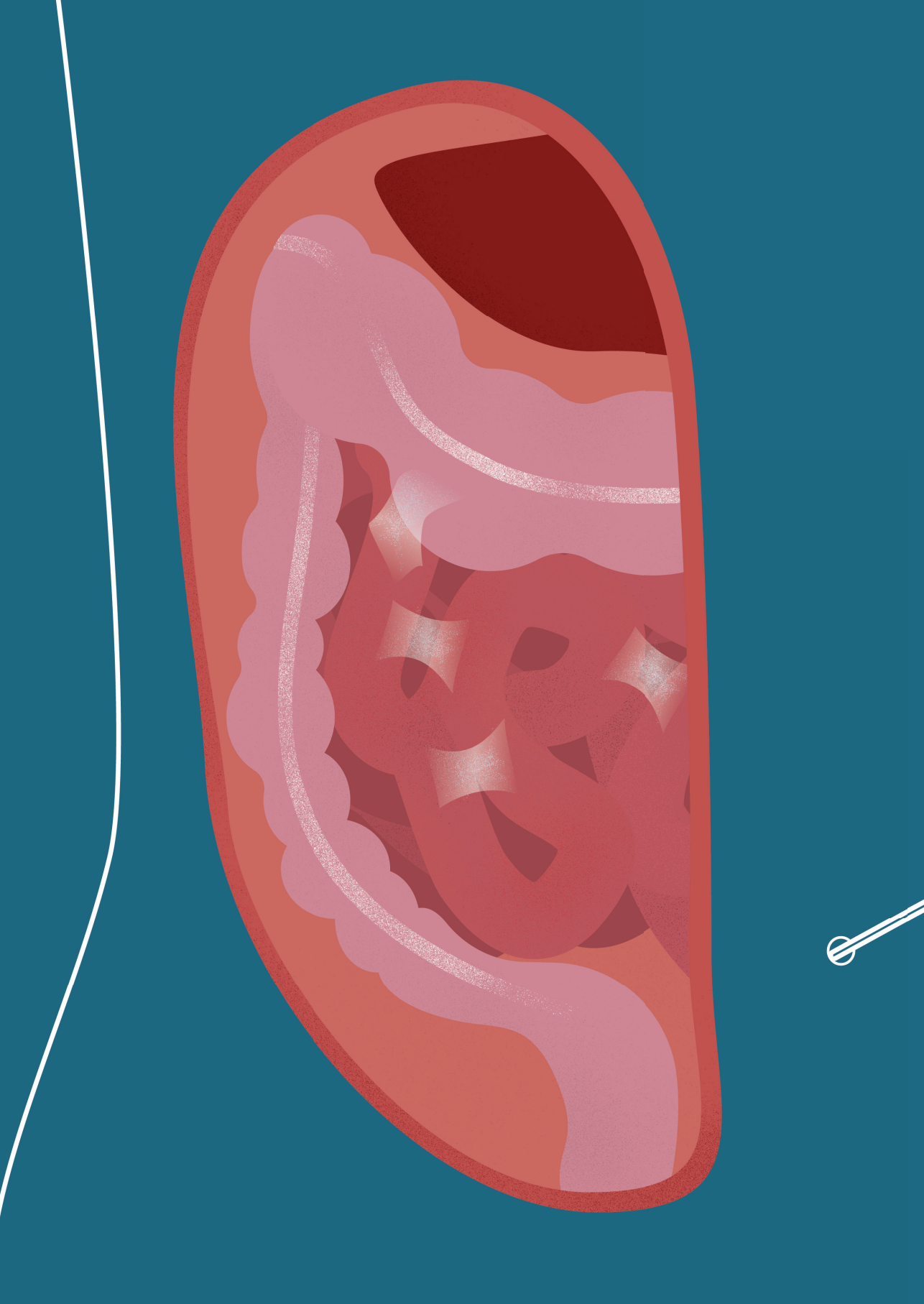
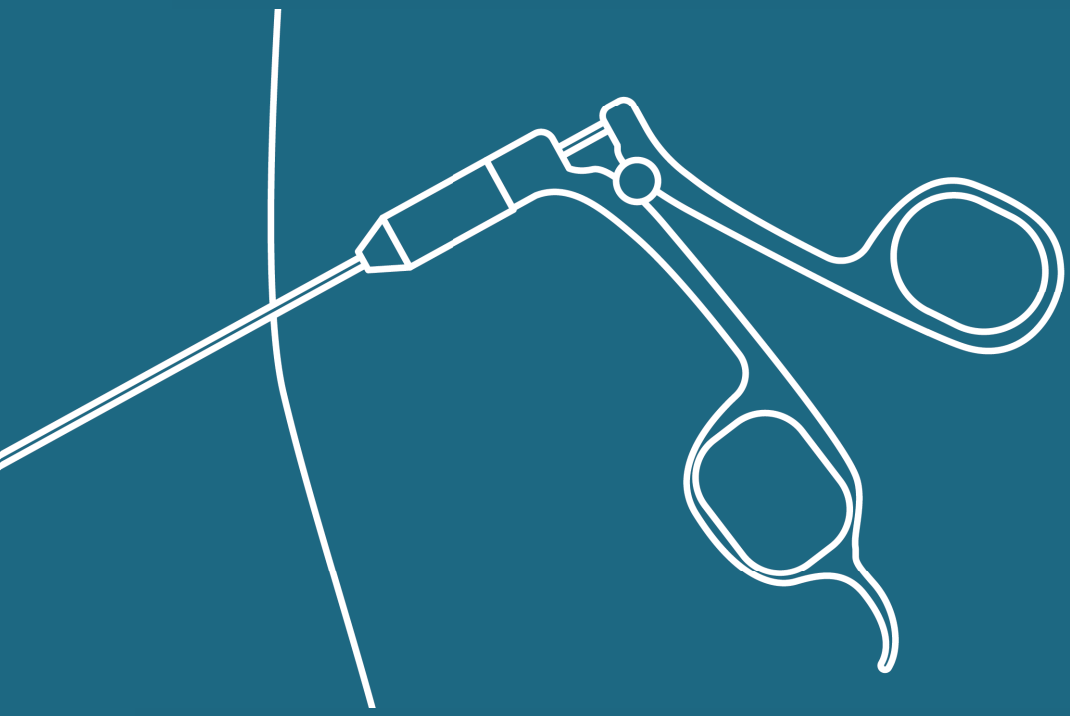


# 7

# Inter-rater agreement of the classification of intra-operative adverse events (ClassIntra®) in abdominal surgery



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Submitted

**Abstract**

*Importance*

Adverse events in surgical patients can occur pre-operatively, intra-operatively and post-operatively. Universally accepted classification systems are not yet available for intra-operative complications. ClassIntra® was recently developed, and seems to be a promising tool for standardized grading of intra-operative events.

*Objective*

The aim of this study is to assess the inter-rater agreement of ClassIntra® and assess its predictive value for post-operative complications in elective abdominal surgery.

*Design, Setting, and Participants*

This study is a secondary use of data from the LAPAD study, a prospective cohort study with detailed data on incidence and management of intra-operative events and post-operative complications. In the LAPAD study data were collected in a well-defined cohort of elective abdominal surgeries. For the purpose of the present study, two teams graded all recorded events according to ClassIntra®.

*Main Outcomes and Measures*

Cohen's Kappa coefficient was calculated to determine inter-rater agreement. Uni- and multivariable linear regression was used to assess the predictive value of the ClassIntra® grade for post-operative complications measured by the Comprehensive Complication Index (CCI®).

*Results*

IAEs were rated in 333/755 (44%) surgeries by team 1, and in 324/755 (43%) surgeries by team 2. Cohen's kappa coefficient for ClassIntra® grades was 0.87 (95% CI 0.84 – 0.90). Discrepancies in grading were most frequent for intra-operative bleeding and adhesions' associated injuries. At least one post-operative complication was observed in 278 (37%) patients. The median CCI® for patients with post-operative complications was 26.2/100 (IQR

20.9 – 39.5). The risk of a post-operative complications increased with every increase in severity grade of ClassIntra®. Intra-operative hypotension (mean difference (MD) 23.41, 95% CI 12.93 – 33.90) and other organ injuries (MD 18.90, 95% CI -4.22 – 42.02) were the strongest predictors for post-operative complications.

*Conclusion and Relevance*

ClassIntra® has a good inter-rater agreement for the classification of iAEs. An increasing grade of ClassIntra® was associated with a higher incidence of post-operative complications. Discrepancies in grading related to common complications in abdominal procedures mostly consisted of intra-operative bleeding and adhesion-related injuries. Grading of interoperative events in abdominal surgery might further improve by consensus regarding the definitions of a number of frequent events.

**Introduction**

In surgery, adverse events and medical errors occur pre-operatively, intra-operatively and post-operatively. Standardized classification of post-operative complications, e.g. using the Clavien-Dindo classification, is widely adopted, and has proven relevant to research and quality improvement programs.[1-3] Prospectively validated classification systems for intra-operative adverse events (iAEs) are not yet broadly adopted.[4-6] IAEs have a major impact at many levels. First, there is an association between iAEs and post-operative outcome.[5,7,8] Second, hospital stays for patients experiencing iAEs are 40 percent more expensive compared with patients without iAEs.[9,10] Third, readmission rates in patients whose surgery is complicated by an iAE are twofold higher.[11]

To improve insight and transparency in outcomes of care, a standardized definition and classification of iAEs is required. A validated score of iAEs facilitates comparability of data from studies, and can be used to assess safety of new surgical techniques and devices, for educational purposes, and for institutional benchmarking. In a recent survey, as many as 77% of all surgeons considered iAEs an important topic in surgery, and endorsed development of a classification for iAEs.[12] However, in a critical appraisal of surgical randomized controlled clinical trials (RCT), less than 10% reported and classified iAEs.[13]

Recently a new and practical classification system for iAEs was proposed, the classification of intra-operative complications (CLASSIC). CLASSIC defines iAEs as any deviation from the ideal intra-operative course occurring between skin incision and skin closure, irrespective of the cause (i.e. technical failures, surgical and anesthesiological difficulties).[12,14] Recently CLASSIC was modified to accommodate 5 grades of severity in analogy to the widely adopted Clavien-Dindo score for post-operative complications, and named ClassIntra®. ClassIntra® was validated in a large multi-center prospective cohort study and showed to be a promising tool for measuring iAEs.[5] However, so far the inter-rater agreement of ClassIntra® has only been assessed in fictious cases and a retrospective pilot study.[5,12]

In the LAPAD (LAParotomy or LAParoscopy and ADhesiolysis) study, intra-operative events, their treatments and consequences were prospectively collected and recorded in detail by

an independent observer.[15] This database provides a unique opportunity to determine the inter-rater agreement of ClassIntra® in a large cohort of elective abdominal surgery.

The aim of this study was to assess the inter-rater agreement of ClassIntra®. The secondary objective was to assess the association between ClassIntra® and post-operative complications in abdominal and pelvic surgery.

## Methods

*Data collection*

This study was conducted using the data from the LAPAD study.[15] In the LAPAD study the incidence and impact of adhesiolysis on intra-operative and post-operative complications was assessed in a cohort of consecutive patients planned for elective abdominal surgery at the Department of Surgery of the Radboud University Medical Center. A total of 755 procedures were included, of which 91% were open procedures. Detailed surgical and anesthesiological intra-operative data were prospectively gathered and entered in a real-time database by a trained physician who was present in the operating theater during all operations. Collected data included any surgical or anesthesiological iAEs and their management. The observer did not take part in the operation. Post-operative complications were registered and scored according to the Clavien-Dindo classification.[16,17] The full protocol of the LAPAD study is described elsewhere (clinicaltrials.gov registration number: NCT01236625).[15]

*Grading of iAEs*

Two teams, team 1 (PK, MS), and team 2 (LG, RB), both consisting of a dedicated and trained researcher and a surgeon, graded all iAEs according to the definitions of ClassIntra® (*table 1)*. The teams were not involved in the development of the score. The teams had access to detailed intra-operative data collected in the LAPAD study, operation reports and anesthesiological reports. The teams were blinded for each other's grading. All

complications and their grading were entered in an Access database (Microsoft office, 2007).

ClassIntra® provides general examples on the grading of several frequent complications.[5] On top of the examples provided by ClassIntra®, the authors felt that pre-arranged definitions for two frequent complications that were not illustrated by an example were inevitable for this study, adhesiolysis and hypotension. Adhesiolysis and hypotension due to bleeding are common in abdominal surgery and have previously been shown to be associated with postoperative complications.[15,18] We defined adhesiolysis as a complication if it took more than 30 minutes or seromuscular injuries occurred, according to relevant literature.[15] The definition of intra-operative hypotension varies in literature, we defined hypotension as a drop of blood pressure of more than 25% of patient-specific normal blood pressure for a period longer than 10 minutes.[19-21] In case of hypotension secondary to a simultaneous extensive bleeding, hypotension was not registered as a separate complication, but regarded a symptom due to extensive bleeding.

*Endpoints*

The primary endpoint of this study was the inter-rater agreement of ClassIntra® as measured by Cohen's kappa. The secondary endpoint was the association between the grade of the most severe iAE and the sum of all post-operative complications, calculated by the Comprehensive Complication Index (CCI®).[22,23] The CCI is a weighted sum of all post-operative complications of one patient, graded by Clavien-Dindo, on a scale from zero to 100, with zero being no post-operative complication and 100 being post-operative death.

*Data analysis*

The inter-rater agreement, calculated by Cohen's kappa coefficient, was interpreted as: slight agreement if $\kappa \leq 0.20$, fair $0.21 \leq \kappa \leq 0.40$, moderate if $0.41 \leq \kappa \leq 0.60$, substantial if $0.61 \leq \kappa \leq 0.80$, almost perfect agreement if $\kappa > 0.80$.[24-26] After the grading of all iAEs by both teams, a meeting was held to discuss discrepancies and reach consensus on the registration and grading of all iAEs. The association between ClassIntra® and post-operative complications was separately analyzed for team 1, team 2 and the consensus between both teams. Uni- and multivariable linear regression analysis was performed to assess the

**Table 1** Classification of iAEs according to ClassIntra®

| Grade | Definition<br>The classification exclusively relates to any event occurring between skin incision and skin closure and should be rated directly after surgery. Any event during the index surgery must be considered, regardless whether it is surgery or anesthesia related.1 Prerequisite: the indication for surgery and the interventions conform to current guidelines. |
|---|---|
| Grade 0 | No deviation from the ideal intra-operative course |
| Grade 1 | Any deviation from the ideal intra-operative course<br>● Without the need for any additional treatment or intervention<br>● Patient asymptomatic or mild symptoms |
| Grade 2 | Any deviation from the ideal intra-operative course<br>● With the need for any additional minor treatment or intervention<br>● Patient with moderate symptoms, not life-threatening and not leading to permanent disability |
| Grade 3 | Any deviation from the ideal intra-operative course<br>● With the need for any additional moderate treatment or intervention<br>● Patient with severe symptoms, potentially life-threatening and/or potentially leading to permanent disability |
| Grade 4 | Any deviation from the ideal intra-operative course<br>● With the need for any additional major and urgent treatment or intervention<br>● Patient with life-threatening symptoms and/or leading to permanent disability |
| Grade 5 | Any deviation from the ideal intra-operative course<br>● With intra-operative death of the patient |

[1] The following events are not defined as intraoperative adverse events: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery or errors in indication



predictive value of the most severe iAE on the sum of post-operative complications. Potential confounders and risk factors for post-operative complications were derived from the LAPAD study; gender, age, body mass index (BMI), alcohol abuse[27], American Society of Anesthesiologists physical status classification (ASA)[28], number of previous abdominal operations, number of previous laparotomies, number of previous laparoscopies, operation site (fore gut/mid or hind gut/other), and adhesiolysis.[15] For multivariable regression analysis, all variables that were related to post-operative complications in univariate analysis ($p<0.2$) or were relevant based on clinical rationale were taken into account. Post-hoc multivariable analysis was performed to determine the impact of the type of iAE (extensive vessel bleeding, diffuse bleeding, accidental ligation of major vessel, extensive

adhesiolysis, bowel injury, other organ injury, other surgical, hypotension, cardiac ischemia) on post-operative complications. For the purpose of this analysis, each patient was assigned to the category of iAE with the highest predictive value for post-operative complications in univariable analysis.

IAEs were classified as being of surgical or anesthesiological origin. A stratified analysis was performed for the association between surgical and anesthesiological iAEs, and post-operative complications.

Statistical analysis was performed using SPSS 25.0 software (SPSS, Chicago, IL, 2018) with a significance threshold of $p<0.05$.

**Results**

During the study period, 844 elective surgeries were eligible, of which 89 were excluded. Reasons for exclusion were cancellation of the operation (n=38), patient declined to participate (n=11), communication difficulties (n=8), miscellaneous (n=32).[15] Seven hundred fifty-five elective surgeries were included in this study. Patient demographics and surgical characteristics are shown in *table 2*.

*Classification*

Team 1 classified 447 iAEs in 333 (44.1%) procedures, team 2 classified 426 iAEs in 324 (42.9%) procedures. In 21 procedures, an iAE was identified only by one team. An overview of all iAEs assessed by both teams and the interventions performed to manage the iAEs is presented in *table 3*.

*Inter-rater agreement*

In 656/755 (86.9%) procedures, there was an agreement in the classification of iAEs according to ClassIntra® grades by both teams, Cohen's kappa 0.87 (95% CI 0.84 – 0.91).

**Table 2** Patient demographics and surgical characteristics

| | |
|---|---|
| **Demographics** | |
| Gender ▪ | |
| Male | 430 (57%) |
| Female | 325 (43%) |
| Age* | 59 ± 14 |
| BMI ▪ | |
| < 20 | 65 (9%) |
| 20 - 25 | 294 (39%) |
| 26 - 30 | 290 (38%) |
| > 30 | 106 (14%) |
| Smoking Status ▪ | |
| Nonsmoker | 267 (35%) |
| Ex-smoker | 340 (45%) |
| Smoker | 147 (20%) |
| Missing | 1 (0%) |
| Alcohol abuse ▪ | |
| Low risk | 711 (94%) |
| Moderate risk | 30 (4%) |
| High risk | 12 (2%) |
| Missing | 2 (0%) |
| Laparotomies in history† | 1 (0-56) |
| Laparoscopies in history† | 0 (0-2) |
| **Pre-operative risk assessment** | |
| ASA classification ▪ | |
| I | 123 (16%) |
| II | 456 (60%) |
| III | 175 (23%) |
| IV | 1 (0.1%) |
| Complexity of surgery ▪, $ | |
| Minor | 2 (0.3%) |
| Moderate | 36 (5%) |
| Large | 445 (59%) |
| Major | 272 (36%) |
| **Characteristics of planned operation** | |
| Open surgery/laparoscopy ▪ | |
| Open surgery | 684 (91%) |
| Laparoscopy | 71 (9%) |
| Anatomical site of primary intervention ▪ | |
| Upper gastrointestinal tract | 83 (11%) |
| Lower gastrointestinal tract | 341 (45%) |
| Hepato-pancreato-billary | 143 (19%) |
| Abdominal wall | 124 (16%) |
| Other | 64 (9%) |
| Surgical experience ▪ | |
| Board-certified surgeon | 524 (69%) |
| Resident | 231 (31%) |

$Based on P-POSSUM score[42], ▪ Number of cases (% of total), * Mean ± standard deviation; † Median (range)

BMI = Body Mass Index, ASA = American Society of Anesthesiologists classification, iAE = intra-operative adverse event

Discrepancies in grading of iAEs comprised different grading of intra-operative bleeding (n=45), bowel injury (n=13), adhesiolysis with serosal injury (n=11), other organ injury (n=10), hypotension (n=8), adhesiolysis (n=3) and cardiac ischemia (n=1).

The consensus process revealed that intra-operative bleeding with transfusion of less than 500cc packed cells was classified grade II. Bleeding requiring more transfusions, or transfusions including platelets or fresh frozen plasma was scored as grade III. Major blood loss during surgery requiring ongoing, extensive transfusion due to persistent hemodynamic instability was scored as grade IV. Adhesiolysis with a bowel injury managed by primary closure was scored as grade II, bowel injuries requiring resection and anastomosis as grade III. Adhesiolysis for longer than 30 min was scored as grade II.

**Table 3** Overview of iAEs and interventions per team

| Complication | Team 1 | Team 2 |
|---|---|---|
| Extensive major vessel bleeding | 18 | 22 |
| Extensive diffuse bleeding | 108 | 98 |
| Accidental ligation of major vessel | 3 | 1 |
| Extensive adhesiolysis | 174 | 202 |
| Bowel injury | 93 | 63 |
| Other organ injury | 24 | 21 |
| Other surgical | - | 2 |
| Hypotension | 26 | 16 |
| Cardiac ischemia | 1 | 1 |
| **Intervention** | **Team 1** | **Team 2** |
| Closure without resection | 173 | 172 |
| Bowel resection and anastomosis | 20 | 17 |
| Ligation of vessel | - | 1 |
| Reconstruction of vessel | 7 | 8 |
| Haemostatic adjuvants | 6 | 9 |
| Splenectomy | 4 | 4 |
| Medicamentous intervention | 57 | 27 |
| Unplanned blood transfusion | 84 | 79 |
| Unplanned ICU admission and stabilization | 3 | 4 |
| Adhesiolysis without need for bowel repair | 83 | 81 |
| Other | 10 | 24 |

iAE = intra-operative adverse event, ICU = Intensive Care Unit

*Association with post-operative complications*

In 278 (36.8%) of all patients post-operative complications were observed. Seventeen patients (2.3%) died during the post-operative period. The median CCI of all patients with post-operative complications was 26.2 (IQR 20.9 – 39.5). In univariable linear regression

analysis using the consensus on grading iAEs, increasing ClassIntra® grade, male gender, increasing age, current smoker (compared with non-smoker), increasing alcohol consumption, increasing ASA score, having a surgical iAE and having an anesthesiological iAE were significantly associated with post-operative complications *(appendix table 1)*. In multivariable linear regression analysis, the severity of iAE was a significant and independent risk factor for a post-operative complication. A higher severity grade of iAE increased the risk of post-operative complications, with a mean difference (MD) in CCI of 5.36 (95% CI 2.29 – 8.42) for grade 2 vs 0, 9.77 (95% CI 4.88 – 14.66) for grade 3 vs 0, and of 16.12 (95% CI 6.44 – 25.80) for grade 4 vs 0. Grade 1 event was only scored in one patient, this patient developed a post-operative complication. Because of the small number of patients with grade 1 iAEs no reliable mean difference could be calculated. Other independent risk factors for post-operative complications were increasing age, increasing ASA score and male gender (*table 4*).

The association between ClassIntra® and post-operative complications separately assessed for team 1 and team 2 showed no major differences in the association between both teams *(appendix table 2,3)*.

Anesthesiological iAEs were registered in 22 (2.9%) procedures, of which 15 (68.2%) were followed by a post-operative complication. Surgical iAEs were recorded in 320 (42.4%) procedures, of which 153 (47.8%) were followed by a post-operative complication. Univariable analysis reported a significant association between anesthesiological iAEs (MD 22.75, 95% CI 14.04 – 31.46) and post-operative complications, as well as surgical iAEs (MD 6.45, 95% CI 3.46 – 9.43) and post-operative complications.

*Post-hoc analysis*

Hypotension was the strongest predictor for any post-operative complications (MD 23.41, 95%CI 12.93 – 33.90). Other organ injury (MD 18.90, 95%CI -4.22 – 42.02), bleeding (MD 9.79, 95%CI 5.04 – 14.53) and adhesiolysis (MD 6.17, 95%CI 2.91 – 9.44) were predictors for post-operative complications.

**Table 4** Multivariable linear regression analysis for the sum of post-operative complications (CCI®)

| Variable | Patients with post-operative complications / total (%) | Mean differences in CCI® (95% CI) | P-value |
|---|---|---|---|
| ClassIntra® grade | | | |
| 0 | 116/420 (27.6%) | Ref. | |
| 1 | 1/1 (100%) | 11.85 (-25.94 – 49.65) | p=0.539 |
| 2 | 106/248 (42.7%) | 5.36 (2.29 – 8.42) | p<0.001 |
| 3 | 43/70 (61.4%) | 9.77 (4.88 – 14.66) | p<0.001 |
| 4 | 12/16 (75.0%) | 16.12 (6.44 – 25.80) | p<0.001 |
| Age | | 0.14 (0.03 – 0.25) | p=0.012 |
| ASA score | | | |
| 1 | 30/123 (24.4%) | Ref. | |
| 2 | 153/456 (33.6%) | 1.25 (- 2. 69 – 5.18) | p=0.535 |
| 3 | 94/175 (53.7%) | 12.36 (7.63 – 17.09) | p<0.001 |
| 4 | 1/1 (100%) | 89.91 (48.67 – 125.14) | p<0.001 |
| Gender | | | |
| Female | 104/325 (32.0%) | Ref. | |
| Male | 174/430 (17.4%) | 3.52 (0.68 – 6.36) | p=0.015 |

CI = confidence interval, ASA = American Society of Anesthesiologists physical status

## Discussion

The high inter-rater agreement found in this study indicates that ClassIntra® is a reliable classification to grade iAEs in general abdominal surgery. In 4 out of 10 abdominal procedures iAEs were registered. An increasing ClassIntra® grade was significantly and independently associated with a higher number of post-operative complications in multivariable analysis. The small differences in the association of ClassIntra® grade with post-operative complications for team 1, team 2 and the consensus show that even though small differences were reported in the grades of iAE, the differences did not change the association with post-operative complications.

ClassIntra® uses broad definitions to describe complications and their management. In the present study extensive adhesiolysis (≥30 min) was defined as an iAE. Reporting adhesiolysis as an iAEs might be somewhat controversial because adhesiolysis is often not perceived as a complication. However, adhesiolysis is an extra surgical procedure not part of the ideal intra-operative course, for which previous studies have reported an association with post-operative sepsis, intra-abdominal complications, and higher hospital costs.[15,29] Even though

adhesiolysis might be inevitable to obtain sufficient exposure to the surgical field, extensive adhesiolysis meets all criteria of an iAE. Adhesiolysis shorter than 30 minutes was not graded as an iAE, as short adhesiolysis also does not seem to have major impact on post-operative outcome.[15] Considering adhesiolysis as an iAE may also contribute to increased awareness of adhesion-related complications during reoperations.

IAE grading partially depends on the intervention performed to manage the complication, similarly to the Clavien-Dindo score. This approach is potentially subject to the preference of surgeons and anesthesiologists. For example, a comparable bowel injury might be managed by primary intestinal closure by one surgeon, while another opts for primary resection, resulting in a different grade.[30] Main reasons for using the intervention performed to grade the severity of the iAE are the following: first, the intervention inflicted is a result of the assessment of the severity by the treating physician. Second, the intervention to treat the complication may influence the post-operative outcome, therefore the impact of an iAE is partly related to their management. Third, details of iAEs are often badly documented, whilst the therapy to treat the iAE is better and more objectively noted, rendering also retrospective assessment easier. In clinical practice, assessment of complications will always depend on the judgment of the treating physician. Nevertheless, uniformity in definition of complications has shown to be crucial for research and quality improvement programs.[1-3]

A major strength of the present study is the use of detailed, prospectively gathered, intra-operative data on adhesiolysis related injuries in general abdominal procedures. Prospective data registration averts the risk of missing data, facilitating reliable grading of iAEs and their management.[31] In a substudy of the LAPAD study, comparing intra-operative observer notes with operative reports, almost 1 in 7 bowel injuries, and 1 in 5 other inadvertent organ injuries were not documented in operative reports.[31] Furthermore, two out of three abdominal procedures today are reoperations, in which exposure to adhesions and subsequently adhesiolysis is very common.[15] Adhesions in abdominal surgery often lead to prolonged operative time and the risk of inadvertent organ injury.[15] In the ClassIntra® validation study, iAEs were reported in 27% of abdominal procedures compared with 22%

of non-abdominal procedures.[5] Detailed data from a study with focus on abdominal adhesiolysis procedures therefore lends itself perfectly for the assessment of iAEs and the inter-rater agreement of ClassIntra® and its predictive value on post-operative complications.

A potential limitation is that the LAPAD study solely included procedures from a tertiary referral clinic. Procedures performed in tertiary referral clinics are often more extensive procedures or anticipated difficult cases, resulting in a higher risk of iAEs. Also, over 90% of procedures performed in the LAPAD study consisted of open procedures, whilst nowadays the about half of abdominal surgical procedures is performed laparoscopically. Laparoscopic procedures are associated with a different risk profile for both intra- and post-operative complications. Laparoscopic surgery is associated with lower blood loss, and a lower risk of iatrogenic splenic injuries.[32,33] On the other hand, laparoscopic surgery is often more dependent on technology, thereby increasing the risk for organisational and equipment related events.[34] Considering post-operative complications, laparoscopic surgery has a lower risk of complications such as superficial surgical site infection, however it does not seem to reduce other severe post-operative complications and mortality.[35] Although risk profiles for laparoscopy and open surgery differ, the multicenter validation study of ClassIntra® demonstrated that a higher grade of iAE incrementally increases the relative risk for post-operative complications. This increase seems consistent throughout different surgical subspecialties and different types of events despite potential differences in risk profile.[5]

Another limitation of our study might be the pre-arranged rules and cut-off points for iAEs on adhesiolysis and hypotension. We applied as few rules as possible for interpreting iAEs, but felt that agreement on some items was inevitable, because definitions in the literature vary. Prior to the classification process, agreement on the classification of adhesiolysis and hypotension was obtained between the teams, without indication of severity according to ClassIntra®. Despite these pre-arranged rules on hypotension and adhesiolysis, classification of both iAEs still resulted in discrepancies in grading between both teams on these iAEs. Post-hoc analysis of the type of iAE showed that both adhesiolysis and

hypotension were strong predictors for post-operative complications. The ClassIntra® is a broad classification using general terms that are applicable to any kind of iAEs. Uniform definitions for common iAEs in abdominal surgery lack, e.g. for hypotension, complicating comparison of iAEs between different institutes. Consensus over the definition of such common events in abdominal surgery might improve overall grading of iAEs.

An earlier initiative in the classifications of iAEs was by Kaafarani et al in 2014.[30,36] There appear to be two major differences between ClassIntra® and Kaafarani.[37] First, the Kaafarani score does not include anesthesiological iAEs. Anesthesiological iAEs are however recorded in 3-41% of all procedures.[5] In our study anesthesiological iAEs were significantly associated with post-operative complications. Second, Kaafarani regards reoperations (e.g. for anastomotic leakage) within 7 days as an iAE, regardless of the fact that they occur post-operatively. Multiple studies have shown associations between post-operative complications such as anastomotic leakage and factors unrelated to surgical injury, such as medication, patient factors, and microbioma[38-41]. Attributing reoperations to an iAE may therefore be an incorrect assumption.

The broad acceptance of the clinical impact of iAEs and the use of standardized classification systems could lead to an increased awareness of iAEs in abdominal surgery, and facilitates comparison of intra-operative outcomes in research. The association between iAEs and post-operative complications might offer possibilities to detect and treat post-operative complications in an earlier stage.



**Conclusions**

ClassIntra® has a high inter-rater agreement and is a reliable tool for the classification of iAEs in daily clinical practice as well as in research settings. This study confirms the association between iAEs and the increased risk of post-operative complications. An increasing grade of ClassIntra® was associated with a higher incidence of post-operative complications. Grading of intra-operative events in abdominal surgery might further improve by reaching consensus on the definitions of a number of frequent events.

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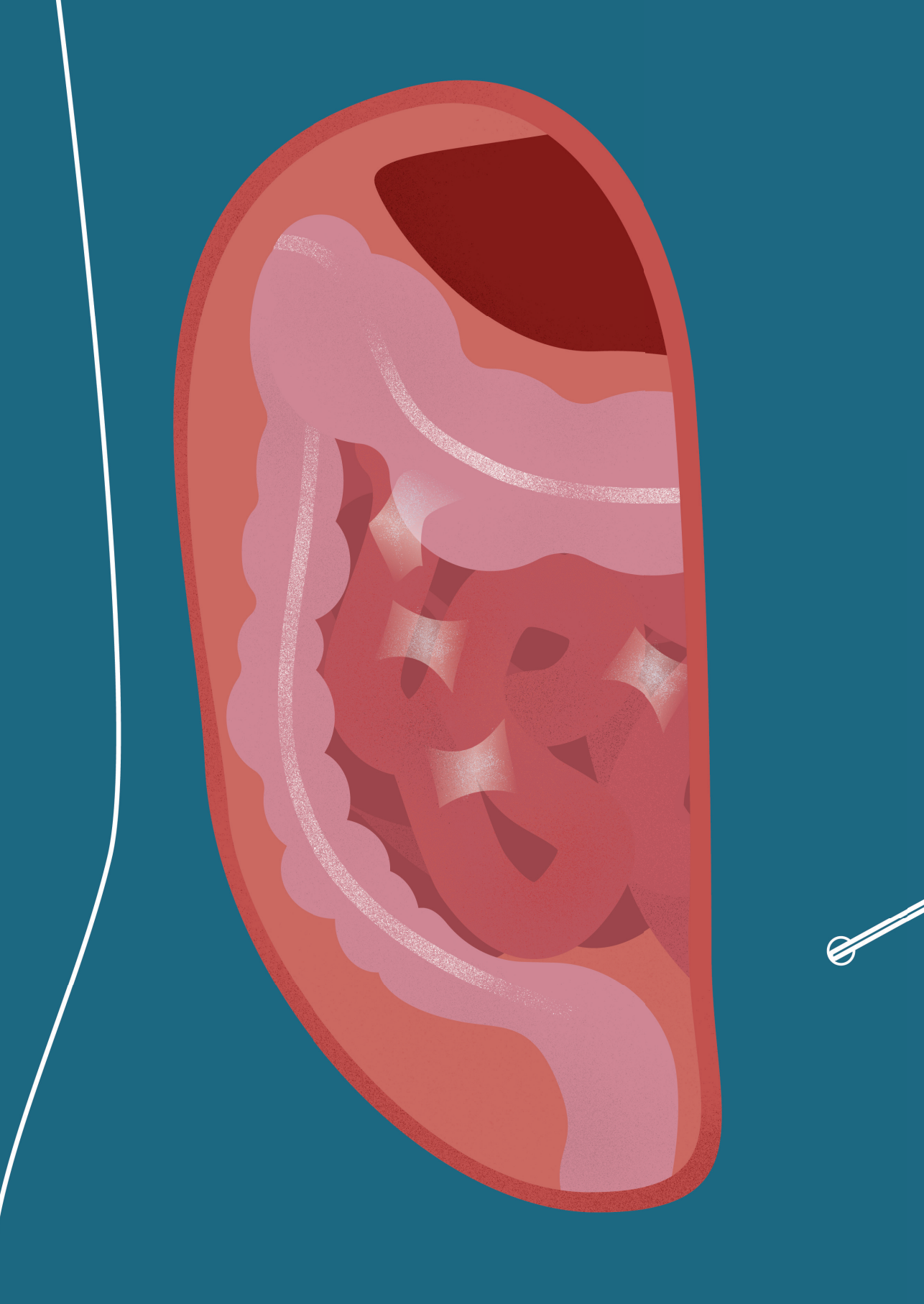
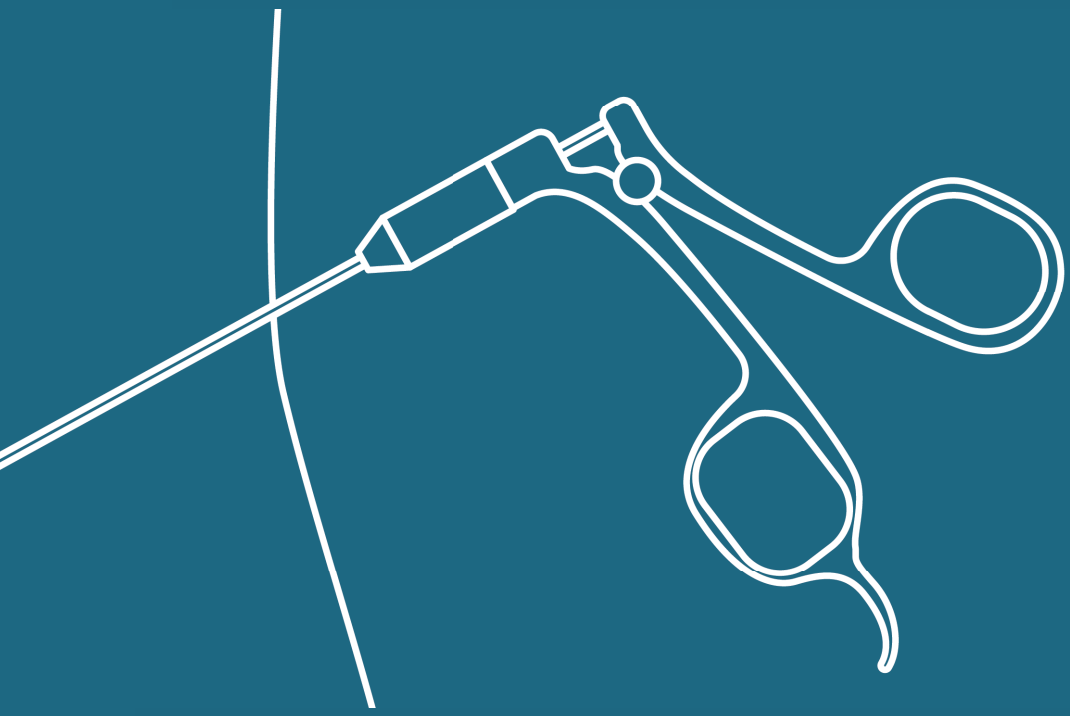


# 8

# Cost-effectiveness of the prevention of adhesions and adhesive small bowel obstruction after colorectal surgery with adhesion barriers: a modelling study



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**Abstract**

*Background*

Adhesion barriers have proven to reduce adhesion-related complications in colorectal surgery. However, barriers are seldom applied. The aim of this study was to determine the cost-effectiveness of adhesion barriers in colorectal surgery.

*Methods*

A decision-tree model was developed to compare cost-effectiveness of no adhesion barrier with the use of an adhesion barrier in open and laparoscopic surgery. Outcomes were incidence of clinical consequences of adhesions, direct healthcare costs, and incremental cost-effectiveness ratio per adhesion prevented. Deterministic and probabilistic sensitivity analyses were performed.

*Results*

Adhesion barriers reduce adhesion incidence and incidence of adhesive small bowel obstruction in open and laparoscopic surgery. Adhesion barriers in open surgery reduce costs compared with no adhesion barrier ($4376 versus $4482). Using an adhesion barrier in laparoscopic procedures increases costs by $162 ($4482 versus $4320). The ICER in the laparoscopic cohort was $123. Probabilistic sensitivity analysis showed 66% and 41% probabilities of an adhesion barrier reducing costs for open and laparoscopic colorectal surgery, respectively.

*Conclusion*

The use of adhesion barriers in open colorectal surgery is cost-effective in preventing adhesion-related problems. In laparoscopic colorectal surgery, an adhesion barrier is effective at low costs.

**Introduction**

Colorectal surgery commonly induces post-operative adhesion formation, causing a lifelong risk for small bowel obstruction, female infertility, and chronic visceral pain.[1–4] Lysis of adhesions at reoperative surgery is associated with inadvertent organ injury, prolonged operative time, and an increased risk of post-operative complications and, therefore, higher costs.[5–7] Several types of adhesion barriers are developed to prevent post-operative adhesion formation after abdominal surgery. In a recent systematic review and meta-analysis on efficacy and safety of adhesion barriers, hyaluronate carboxymethylcellulose (HA/CMC) was proven to safely reduce the incidence of site-specific adhesions and the incidence of re-operations for adhesive small bowel obstruction after open colorectal surgery.[8] However, despite the burden of post-operative adhesions, and the proven benefit of adhesion barriers, they are seldom applied. In a nationwide survey carried out in the Netherlands in 2009, just 13.4% of surgeons indicated that they had used any adhesion barrier in the previous year and a recent follow-up survey did not report much subsequent change.[9,10] Doubts about cost-effectiveness and the need for adhesion prevention in minimally invasive surgery may explain the reluctance in the use of barriers. Previous cost-effectiveness analyses of adhesion barriers have been based on costs of adhesion-related re-admissions and only concern open surgery.[11,12] The efficacy data used were derived from second-look surgery studies, with a suggested 25–50% reduction in the number or density of adhesions with the use of a barrier.[11,12] In the absence of data on reduction of adhesion-related readmissions with the use of a barrier, costs were extrapolated from the reduction of adhesions. Since publication of these analyses, evidence on both the burden of adhesions and the effectiveness of adhesion barriers has increased substantially. Earlier, a re-admission for postoperative small bowel obstruction was considered the most important complication.[13] New evidence has clearly shown that difficulty due to dissecting adhesions at repeat abdominal surgery is an even bigger problem.[14] Moreover, evidence on efficacy of adhesion barriers is no longer limited to adhesion incidence, but comprises clinically relevant endpoints.[8]

A decision-tree model was developed in this study for the use of an adhesion barrier in open colorectal surgery and laparoscopic colorectal surgery, based on the best available evidence

and considering cost and effect. The model was designed as an important contribution towards creating an evidence-based, decision-making protocol on the use of adhesion barriers in colorectal surgery.

**Material en methods**

*Decision model*

A decision-tree model was designed with Microsoft Office Excel 2007 that evaluated the strategy of adhesion prevention with an adhesion barrier in both open and laparoscopic colorectal surgery. A decision-tree model is a simplified framework of complex real-life processes that uses a mathematical method to weigh the risks, benefits, and costs of clinical strategies.[15] In the model, two strategies are compared: (1) current clinical practice, colorectal surgery without the use of an adhesion barrier, and (2) colorectal surgery with the use of an adhesion barrier (Fig. 1).

Hypothetical cohorts of patients, who have undergone colorectal surgery (open or laparoscopic), were distributed over the different pathways in the decision-tree, based on a set of probabilities that were derived from recently published systematic reviews and observational and intervention studies. This allowed the synthesis of evidence and, thereby, evaluation of the effects and adhesion-related healthcare costs determined by the treatment decision.

Adhesive small bowel obstruction (ASBO) and difficulties at reoperation were included in the model as potential consequences of adhesions. Female infertility and chronic visceral pain were not considered. Risk of infertility is only an additional reason for the use of an adhesion barrier in a very small and specific subgroup. Regarding chronic visceral pain, no consistent evidence is available on etiology, incidence, and costs after colorectal surgery.[4]

*Population*

The two target populations consist of patients who undergo a colorectal resection for a benign or malignant indication, by either an open or laparoscopic surgical approach. Colorectal resection is commonly performed for various indications; the main indication is colorectal cancer.[16] Colorectal surgery has a relatively high incidence of postoperative adhesion formation.[14,17] In 2016, in more than 85% of colorectal cancer resections performed in the Netherlands, laparoscopic techniques were used.[18] There is recent evidence that laparoscopy is associated with a lower incidence of adhesions, particularly to the abdominal wall.[19,20]

*Probabilities*

In the model, the hypothetical cohorts of patients, who underwent a colorectal resection, with or without the use of an adhesion barrier, have different probabilities for the development of adhesions and subsequent development of ASBO, operative or conservative treatment for ASBO, and adhesiolysis at future repeat surgery. Probability estimates were derived from recent literature (Table 1).[8,19,21–32]

PubMed, Embase, and the Cochrane Library were searched for relevant literature. Risk ratios for adhesions, ASBO, and operative treatment of ASBO, with the use of an adhesion barrier, are based on efficacy data for HA/CMC, as this is the only form of adhesion barrier with consistent evidence available on adhesion prevention in visceral surgery. HA/CMC is not easily applicable in laparoscopic surgery, and evidence for laparoscopy is lacking. Since there are no alternative barriers with sound evidence on safety and efficacy in laparoscopic colorectal surgery, efficacy data of HA/CMC in open colorectal resection was extrapolated to the laparoscopic model. The data on incidence of adhesions after open and laparoscopic colorectal surgery were derived from a recently published multicenter study.[19] In this study, adhesions after open and laparoscopic colorectal cancer surgery are compared during surgery for liver metastases.

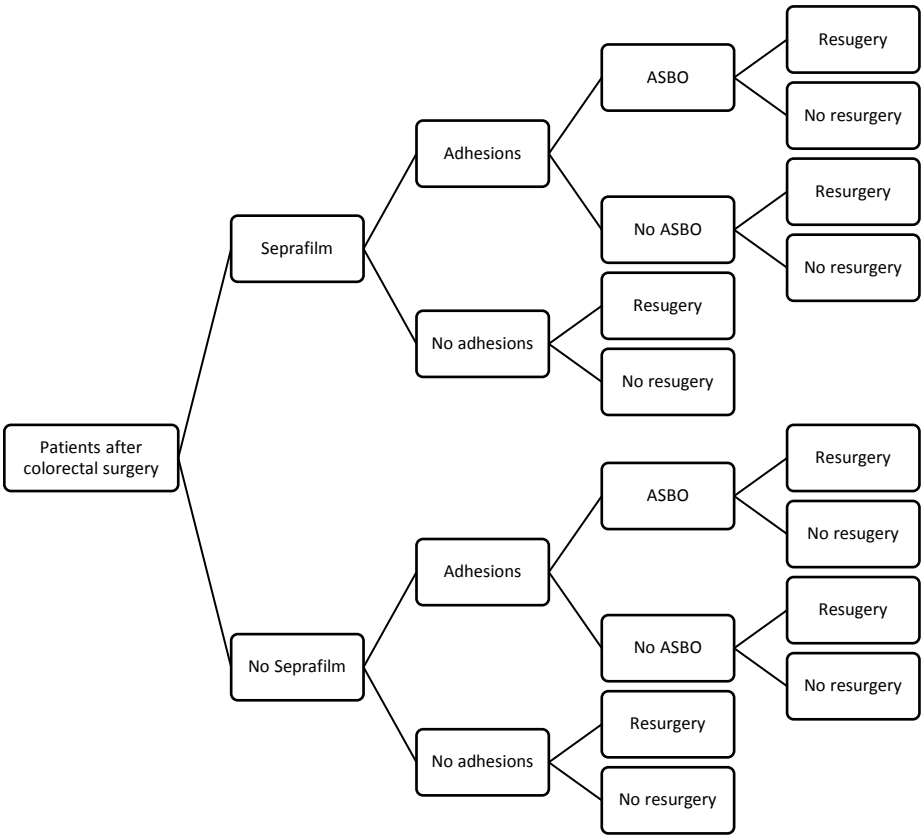


**Figure 1** Decision-tree model for evaluation of the use of an adhesion barrier in colorectal surgery

In a recent systematic review on the value of adhesion barriers, there were no data on the total incidence of adhesions with the use of HA/CMC.[8] A new search yielded no additional data on the total incidence of adhesions with the use of HA/CMC. Thus, adhesion incidence with HA/CMC was derived from the incidence of site-specific adhesions reported (i.e. midline, pelvic adhesions), by only including the anatomical site with the highest incidence of adhesions from each study.[21–23] The peristomal site was not considered relevant for total adhesion formation after colorectal surgery. The efficacy is expressed as a risk ratio of adhesions with the use of HA/CMC versus no adhesion barrier (RR 0.51 [95% CI 0.43 – 0.61]).

**Table 1** Input probabilities in decision-tree model

| | Open | | | Laparoscopic | | | | Adhesion barrier strategy | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Probability | α | β | Probability | α | β | Ref. | RR | 95%CI | Ref. |
| Patients with adhesions | 0.889 | 80 | 10 | 0.623 | 38 | 23 | 19 | 0.51 | 0.43-0.61 | 8, 20-22 |
| Patients with ASBO 4 years | 0.086 | 199 | 2127 | 0.066 | 77 | 1085 | 23-30 | 0.68 | 0.35-1.32 | 8, 20-22 |
| Patients with ASBO treated surgically | 0.032 | 74 | 2252 | 0.031 | 36 | 1126 | 23-30 | 0.49 | 0.28-0.88 | 8, 20-22 |
| Patients with repeat surgery 4 years | 0.208 | 64 | 200 | 0.209 | 64 | 200 | 31 | | | |

α = patients with event; β = patients without event; RR = relative risk; CI = confidence interval; ASBO = adhesive small bowel obstruction

The probability of ASBO and the probability of surgery for ASBO after colorectal surgery were derived from an update of the systematic review on the burden of adhesions after abdominal surgery (1990 to June 2016).[24–31] Weighted mean follow-up of the studies was 55.3 months. The probability of future repeat abdominal surgery was derived from a recently published, prospective cohort of patients, who underwent elective abdominal surgery.[32] This cohort comprises mainly patients operated by open approach. Since the incidence of repeat abdominal surgery is not expected to be substantially different for patients operated on by laparoscopy or by open approach, the probability used in both arms of the model is based on the total cohort. In the 4 years following initial lower gastrointestinal tract surgery, 24% of patients underwent repeat abdominal surgery, including re-operations for ASBO. In the model, re-operations for ASBO were subtracted from the probability for repeat surgery to ensure that these re-operations were not included twice in the model.

Costs

An analysis of adhesion-related costs was performed with a healthcare perspective, including only direct healthcare costs for treatment (Table 2). All monetary values are presented in US dollars (USD/$). Euros were converted to USD using the exchange rate: 1 Euro to 1.1264 USD.

The mean number of films per patient reported in two of the three studies on adhesion prevention with HA/CMC in colorectal surgery was 3.3 films. The total costs for HA/CMC were based on the use of 3.3 films and the price of a HA/CMC film in 2016 in the Netherlands, adding up to a total cost of $629.68.[21,33] For sensitivity analysis, a Beta-PERT distribution was assigned for the number of sheets per patient, ranging between 2 and 4. Costs of the barrier were varied according to the Beta-PERT distribution ($382–$763), Table 2.

The healthcare costs of ASBO were derived from a recently performed retrospective analysis of patients admitted to the Radboud University Medical Center with the diagnosis of ASBO.[34] The costs for repeat surgery were derived from a recent, large, cohort study on adhesiolysis- related morbidity in abdominal surgery.[5]

Data analysis

Data were analysed using mean values for a base case analysis, to obtain percentages of ASBO, re-operation for ASBO, patients with adhesions, and direct healthcare costs for the two strategies, in the 4 years following colorectal surgery. The time frame was based on the mean 4 years' follow-up periods of the studies, which underlie the probabilities for ASBO and repeat surgery. If the use of an adhesion barrier was more effective and more expensive, incremental cost-effectiveness ratios (ICER) were calculated to determine the additional costs for one patient, in whom adhesion formation was prevented. All presented ICERs are a comparison of the adhesion barrier strategy versus no barrier. If the adhesion barrier strategy was more effective and reduced costs, this was considered dominant, and ICERs were not calculated. A base case analysis was conducted for the two strategies in open and laparoscopic surgery separately. Probabilistic sensitivity analysis was performed,

**Table 2** Costs used in the model

| | Value | SD | Reference |
|---|---|---|---|
| Costs HA/CMC | $ 630 | $ 382 - $ 763* | 20, 32 |
| ASBO with operative treatment | $ 18366 | $2 831 | 33 |
| ASBO with non-operative treatment | $ 2565 | $ 299 | 33 |
| Repeat surgery - no adhesions | $ 14063 | $ 812 | 5 |
| Repeat surgery - adhesions | $ 18579 | $ 1 722 | 5 |

HA/CMC = hyaluronate carboxymethylcellulose; ASBO = adhesive small bowel obstruction; SD = standard deviation

* For the number of sheets per patient a Beta-PERT distribution was assigned, ranging between 2 and 4.

using a Monte Carlo simulation, to explore the impact of uncertainties in the model parameters, as shown in Tables 1 and 2. In the Monte Carlo simulation, 5000 samples were drawn from the parameter distributions. For each sample, the hypothetical patient cohort was run through the model based on these sampled parameters, representing the uncertainty in the cost-effectiveness estimation. Lognormal distributions were used for all risk ratios; beta distributions for probabilities and costs were described by normal distributions. Confidence intervals were calculated from the probabilistic sensitivity analysis using the percentile method.

In addition, threshold analyses were conducted for the costs of the adhesion barrier and the probability of repeat surgery, in order to find the maximum values for these parameters at which the adhesion barrier saves costs. Deterministic sensitivity analysis was conducted to explore the influence of deviation in the efficacy of the different parameters on the cost-effectiveness, assuming all other variables to be fixed. All parameters were individually changed to their lower and upper boundaries of the 95% confidence intervals. Results of the analysis are presented in a tornado diagram. Furthermore, a best- and worst-case scenario was calculated; for the worst-case scenario, the risk ratios for adhesions, ASBO,

and operative treatment of ASBO were all set to the upper limit of their confidence interval (Table 1). For the best-case scenario, all three risk ratios were raised to the lower limit of their confidence interval.

**Results**

*Best case analysis*

With the parameters at their base case values, for the open colorectal surgery cohort, the adhesion barrier strategy was both more effective and less expensive than the no adhesion barrier strategy, whilst in the laparoscopic colorectal surgery cohort, the adhesion barrier strategy was more effective, but more expensive (Table 3). In open colorectal surgery, use of an adhesion barrier reduced the incidence of adhesions from 88.9% (95% CI 81.8 – 94.5%) to 45.3% (95% CI 37.3 – 54.6%) and the incidence of ASBO from 8.6% (95% CI 7.5 – 9.7%) to 6.2% (95% CI 2.9 – 11.3%). The expected mean direct healthcare costs in 4 years after initial open colorectal surgery were reduced by $106, from $4482 (95% CI $3074 – $6284) per patient in the group without an adhesion barrier to $4376 (95% CI $3140 – $5892) in the group with an adhesion barrier. After laparoscopic colorectal surgery, the incidence of patients with adhesions was reduced from 62.3% (95% CI 49.9 – 73.8%) to 31.8% (95% CI 24.3 – 40.7%) and the incidence of ASBO from 6.6% (95% CI 5.2 – 8.1% ) to 4.5% (95% CI 2.2 – 9.2%) with an adhesion barrier. Costs increased by $163 per patient when an adhesion barrier was used. Direct health care costs over 4 years after laparoscopic colorectal surgery for the adhesion barrier group were $4482 (95% CI $3031 – $5591) versus $4320 (95% CI $2881 – $5709) for the no adhesion barrier group. In open colorectal surgery, the adhesion barrier strategy dominated the current, no-adhesion barrier practice. For laparoscopic colorectal surgery, the ICER for one patient with adhesions prevented was $123. Cost reduction for both open and laparoscopic colorectal surgery is mainly due to the reduction of readmissions for ASBO in the adhesion barrier arm. Reduction of costs is also due to the prevention of adhesions at reoperation and therefore reduction of operative time with a decrease of time needed for adhesiolysis.

**Table 3** Results of base-case and deterministic sensitivity analysis in the open- and laparoscopic surgery cohorts

| Strategy | Costs | Percentage adhesions | Percentage ASBO | Costs per patient with adhesions prevented |
|---|---|---|---|---|
| **Open cohort** | | | | |
| Baseline | | | | |
| No barrier | $4474 | 88.9% | 8.6% | |
| Barrier | $4372 | 45.3% | 5.8% | Dominant |
| Best-case scenario | | | | |
| No barrier | $4474 | 88.9% | 8.6% | |
| Barrier | $4129 | 38.2% | 3.0% | Dominant |
| Worst-case scenario | | | | |
| No barrier | $4474 | 88.9% | 8.6% | |
| Barrier | $4789 | 54.2% | 11.3% | $908 |
| **Laparoscopic cohort** | | | | |
| Baseline | | | | |
| No barrier | $4179 | 62.3% | 6.6% | |
| Barrier | $4220 | 31.8% | 4.5% | $135 |
| Best-case scenario | | | | |
| No barrier | $4179 | 62.3% | 6.6% | |
| Barrier | $4016 | 26.8% | 2.3% | Dominant |
| Worst-case scenario | | | | |
| No barrier | $4179 | 62.3% | 6.6% | |
| Barrier | $4576 | 38.0% | 8.7% | $1663 |

*Sensitivity analysis*

The results of the probabilistic sensitivity analysis are shown in Fig. 2a and b. The Monte Carlo simulation showed that the use of an adhesion barrier is always more effective in preventing adhesions and ASBO, for both open and laparoscopic colorectal surgery. The use of an adhesion barrier had a 66% probability of reducing costs in the open surgery cohort. In the laparoscopic surgery cohort, the probability was 41%. Threshold analysis in the open colorectal surgery cohort showed that using a barrier priced at $736 (95% CI $305 – $1187) or more no longer reduces costs. The same effect was seen with the re-operation rate lowered to 16% (95% CI 1 – 74%) or less. In the laparoscopic surgery cohort, the thresholds for cost-reduction with an adhesion barrier were a price of $592 (95% CI $256 – $954) and a reoperation rate of 24% (95% CI 3 – 100%).

Results of the deterministic sensitivity analysis are shown in Fig. 3a and b. Variation of the costs of the adhesion barrier had the largest effect on the ICER for one patient with adhesions prevented in open and laparoscopic surgery. In the best-case scenario, applying an adhesion barrier in both open and laparoscopic colorectal surgery reduces costs. In the worst-case scenario, the ICER for one patient with adhesions prevented is $908 in the open colorectal surgery patient cohort and $1663 in the laparoscopic colorectal surgery patient cohort, Table 3.

**Discussion**

The routine use of an adhesion barrier in open colorectal surgery is cost-effective, considering a 4-year time frame. Whilst in laparoscopic colorectal surgery, the expenses are only $163 per patient, and the additional costs for one patient with adhesions prevented are $123. The findings in the present study are in agreement with a comparable study, which demonstrated cost savings in all types of open abdominal surgery and potential cost-effectiveness in major laparoscopy.[35]

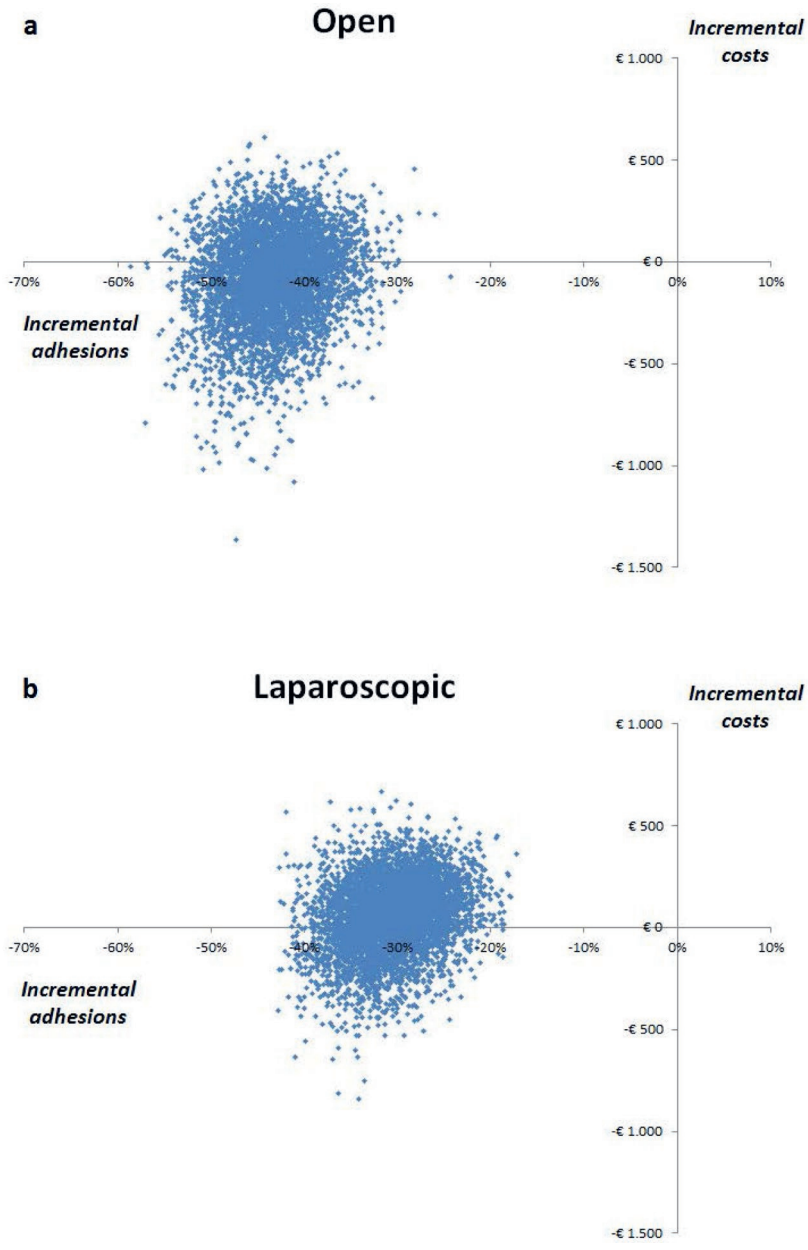


**Figure 2 A** Scatter plot of Monte Carlo Simulation for open colorectal surgery, displaying costs (y-axis) and effect (x-axis) of adhesion barrier strategy. **B** Scatter plot of Monte Carlo Simulation for laparoscopic colorectal surgery, displaying costs (y-axis) and effect (x-axis) of adhesion barrier strategy.

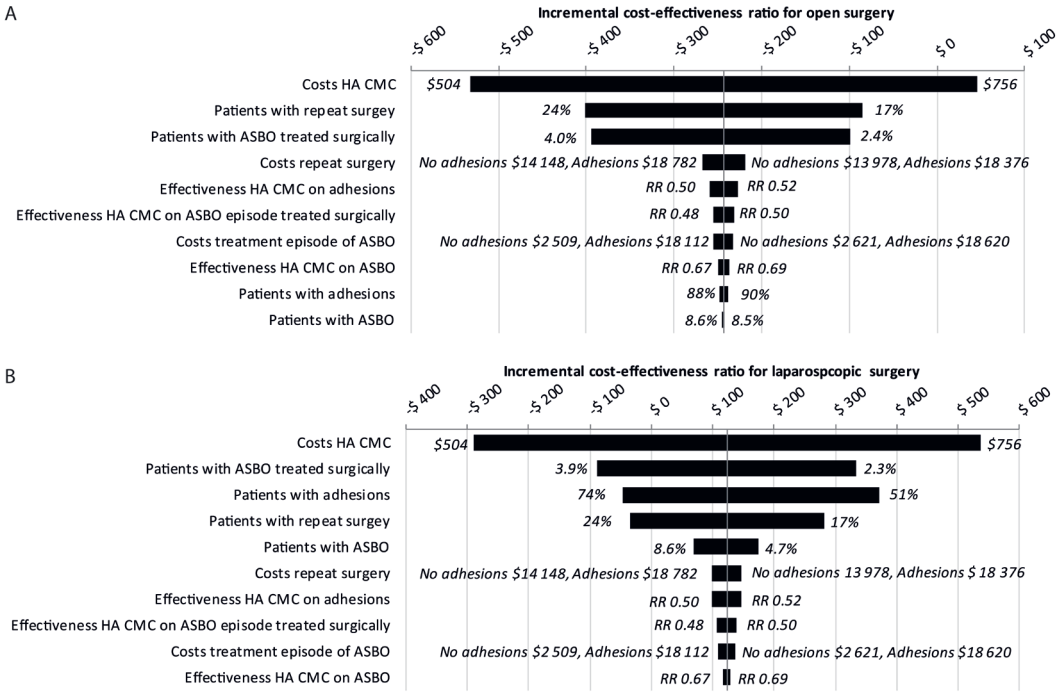


**Figure 3 A** Tornado diagram of variation of individual parameters in open colorectal surgery. **B** Tornado diagram of variation of individual parameters in laparoscopic colorectal surgery

The present study has the advantage that it concerns a homogenous group of patients with a high risk of post-operative adhesion formation. This well-defined population enhances the clinical applicability of the results. In addition, more recent cost data are used in the present model, of which the majority were specifically for colorectal surgery. Costs are twice as much for operative treatment of ASBO and for the adhesion barrier compared with costs reported previously. A comparable underestimation of costs for the adhesion barrier and ASBO treatment was found in other cost-effectiveness reports from earlier this century.[11,12] The most important limitation of previous studies is the lack of evidence on efficacy of adhesion barriers in reducing adhesion-related complications.

The major strength of the present study is that the recently generated evidence for the burden of adhesions and the efficacy of adhesion barriers in colorectal surgery could be synthesized. We synthesized all available evidence to show the expected consequences of adopting adhesion barriers on both costs and effects, as well as the impact of the uncertainty due to a lack of evidence regarding these consequences. A limitation is the need to extrapolate data on the efficacy of adhesion barriers from open to laparoscopic colorectal surgery, due to scarce and inconsistent evidence with other formulas of HA/CMC (e.g. slurry made of film and spray) in laparoscopy.[36–38] A deviating efficacy in laparoscopy would be highly relevant, particularly, because the majority of colorectal resections are currently performed by laparoscopy.[18] In the worst-case scenario, assuming reduced effectiveness of the adhesion barrier (RR 0.61) resulted in an ICER of $908 in the open surgery cohort and $1633 in the laparoscopic surgery cohort, which for laparoscopy is more than a tenfold increase compared to base case analysis. Therefore, the modelled risk ratio (0.51) of adhesions with the use of an adhesion barrier should serve as reference standard for the development of novel adhesion barriers for laparoscopic use.

With the rise of laparoscopy in colorectal surgery, open surgery is almost exclusively performed in cases that are not suited for a laparoscopic approach. One of the reasons for an open approach could be problems with adhesions during laparoscopic surgery. Open cases are therefore more prone to postoperative complications.[5] This example illustrates the need for adhesion barriers in both laparoscopic and open surgery, to prevent future problems at repeat surgery.

The time frame, within which the model applies, was limited to 4 years, whilst adhesion-related complications or repeat surgery may occur many years later.[13] However, approximately 60% of ASBO occurs within the first 4 years after lower abdominal surgery[13]; there is no data available for repeat surgery. Using a longer time frame would increase ASBO and repeat surgery rate, thereby potentially increasing the clinical benefit and cost-effectiveness of the adhesion barrier strategy.

Female infertility and chronic visceral pain, which are known consequences of adhesions, were not included in the model. Risk for infertility is only applicable to a small group of

female patients undergoing colorectal surgeries at a young age. No consistent evidence is available regarding chronic visceral pain, and most costs are generated outside the hospital.[4] The incompleteness of the model for these adhesion-related complications may have caused underestimation of adhesion-related costs, and thus an underestimation of the cost-effectiveness of the use of adhesion barriers.

The model took into account the costs of repeat surgery depending on the presence of adhesions, and not the extent and severity of adhesions. Evidence shows that laparoscopic approach and use of an adhesion barrier reduce the incidence of adhesions and their extent and severity.[8,19] Although reduction of extent and severity of adhesions potentially decreases adhesiolysis related complications and costs, the evidence was insufficient to consider including these variables in the model.[5] Excluding the efficacy and costs related to reduction in severity and extent may have resulted in an overestimation of the adhesion-related costs in the laparoscopic surgery cohort and an underestimation of the benefit of an adhesion barrier in both cohorts.

The costs of an adhesion barrier were based on the unit costs in the Netherlands in 2016. The unit costs may change according to the volume of products required. Variation of the costs of an adhesion barrier had the largest influence in our model, Fig. 3a and b. Higher volumes may result in a lower unit cost, favouring the cost-effectiveness of the use of adhesion barriers in colorectal surgery.

Due to a higher life expectancy and advances in surgical technology, an increasing number of patients undergo abdominal surgery multiple times during their lifetime.[32] Adhesion formation is the most common long-term complication of abdominal surgery, and prevention of adhesion formation from initial abdominal surgery is the critical step in breaking the sequence of complications due to adhesions. Despite evidence of reduced adhesion formation with the application of adhesion barriers, adhesion barriers are seldom used in practice. Doubts about cost-effectiveness and the need for adhesion prevention in the 'minimally invasive era' probably underlie this reluctance.[9] The present cost-effectiveness analysis is based on the best evidence available for both open and laparoscopic colorectal surgery and can, for open colorectal surgery at least, remove these

doubts. Since the use of an adhesion barrier in laparoscopic colorectal surgery involves extra costs, data on quality-adjusted life-years (QALYs) are required to value the benefits of adhesion barriers and to compare the costs per unit of effect gained to a cost-effectiveness threshold.[39] In order to determine QALYs for adhesions and the use of adhesion barriers, future research should address patient-reported outcomes (PROs), such as functional status and quality of life. It is conceivable that adhesion-related complications will have a negative impact on PROs.[40]

**Conclusion**

The use of an adhesion barrier in open colorectal surgery will probably result in cost savings, and in laparoscopic colorectal surgery, this might be accompanied by limited additional costs. For laparoscopic colorectal surgery, more evidence on adhesion barriers is a prerequisite for clinical implementation.

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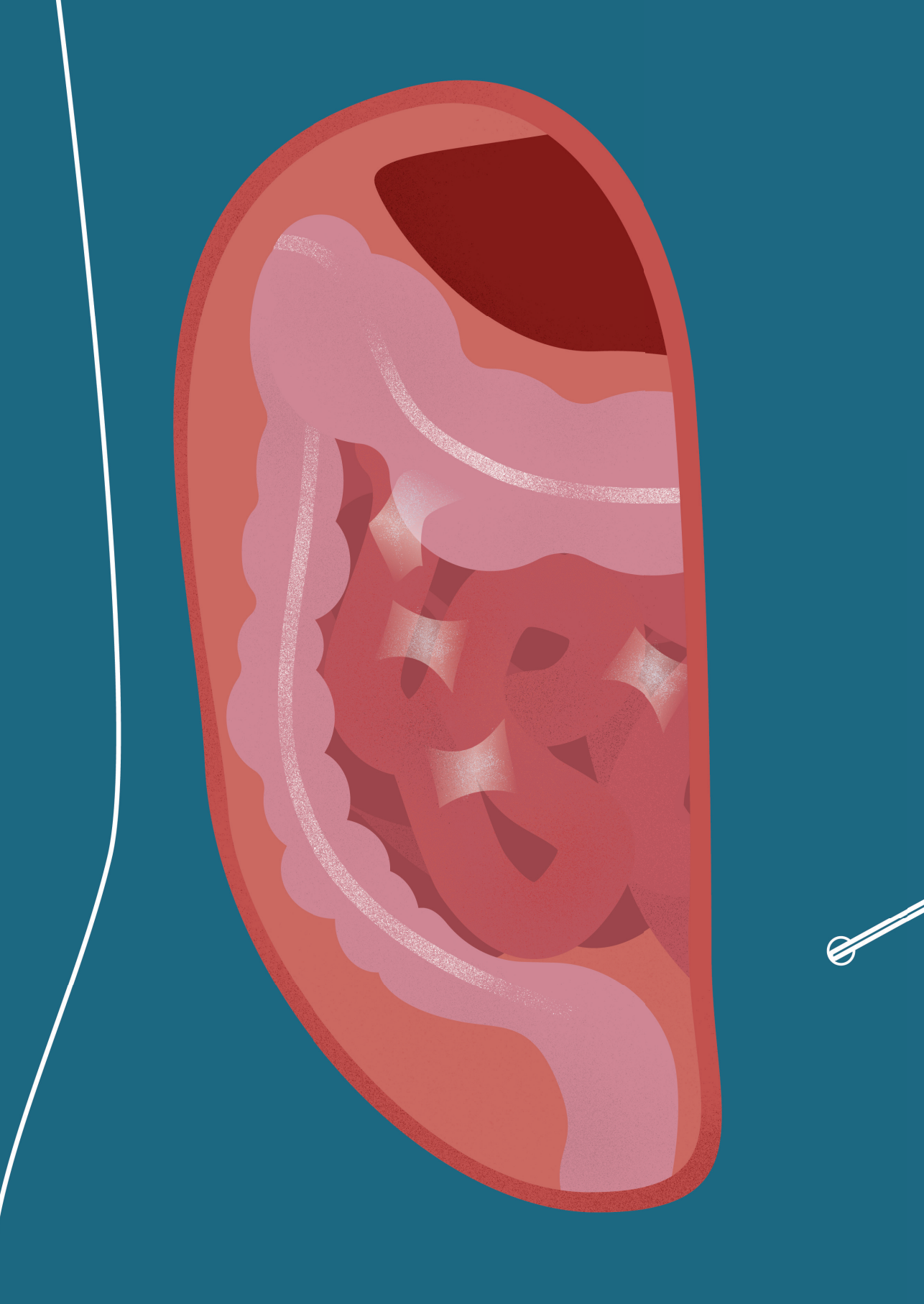
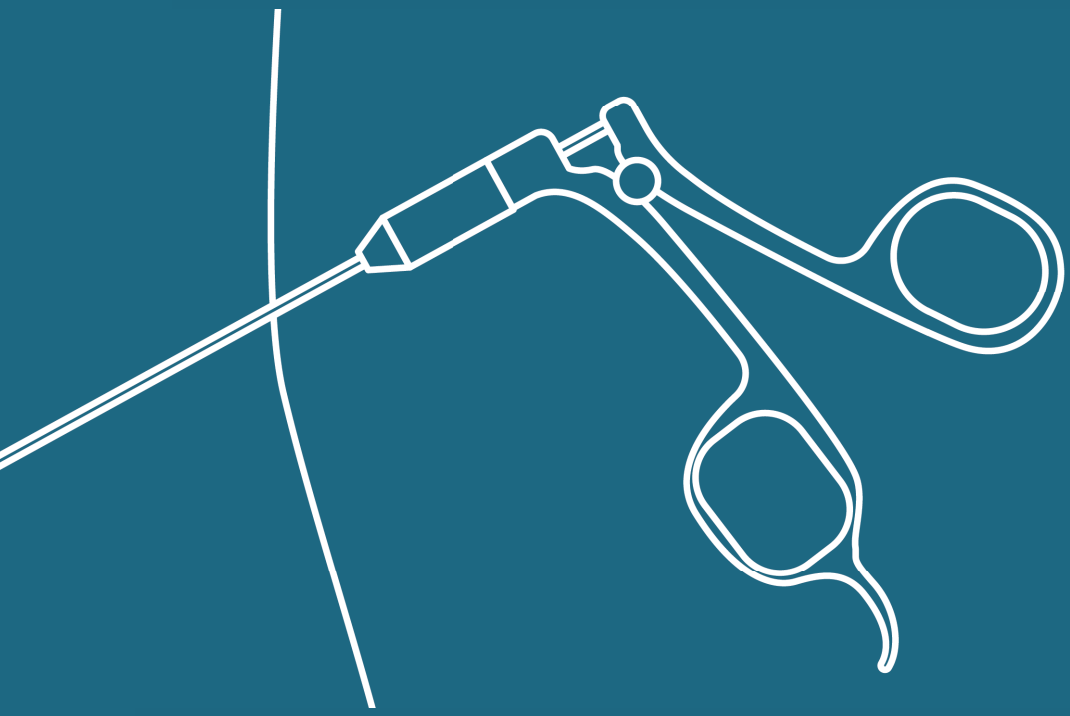


# 9

# Adhesive small bowel obstruction in the minimally invasive era

## General discussion



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**Abstract**

Roughly 60% of all cases of small bowel obstruction are caused by adhesions. Adhesions are a form of internal scar tissue, which develop in over 45–93% of patients who undergo abdominal surgery. With this relatively high incidence, the population at risk for adhesive small bowel obstruction (ASBO) is enormous. Minimally invasive surgery reduces surgical wound surface and thus holds promise to reduce adhesion formation. The use of minimally invasive techniques results in a 50% reduction of adhesion formation as compared with open surgery. However, since ASBO can be caused by just a single adhesive band, it is uncertain whether a reduction in adhesion formation will also lead to a proportional decrease in the incidence of ASBO. Minimally invasive surgery might also improve operative treatment of ASBO, accelerating gastro-intestinal recovery time and lowering the risk of recurrent ASBO associated with adhesion reformation. We will discuss recent evidence on the impact of minimally invasive surgery on the incidence of ASBO and the role of minimally invasive surgery to resolve ASBO. Finally, we will debate additional measures, such as the use of adhesion barriers, to prevent adhesion formation and adhesion-related morbidity in the minimally invasive era.

## 1. Introduction

As many as 60% of all episodes of small bowel obstruction (SBO) are caused by adhesions.[1] Adhesions are attachments of abdominal structures by internal scar tissue that are the result of healing of the peritoneum after it has been damaged, in most cases by surgery.[2] Adhesions can be filmy or dense and be present as an isolated band or as a 'curtain' or tangle with difficulty recognizing visceral structures. The degree of density and vascularization is traditionally classified using the Zühlke classification (Table 1).[3] A more comprehensive and clinically relevant classification including projected locations of adhesions is the Peritoneal Adhesion Index (PAI) (Figure 1).[4,5]

**Table 1** Zühlke classification

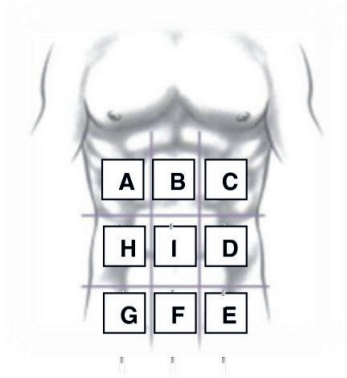
| Grade | Description |
|---|---|
| 0 | No adhesions or insignificant adhesions |
| 1 | Adhesions that are filmy and easy to separate by blunt dissection |
| 2 | Adhesions with beginning vascularization that can be dissected blunt but some sharp dissection is necessary |
| 3 | Adhesions with clear vascularization that can only be dissected using sharp dissection |
| 4 | Adhesions which strongly attached organs, dissection is only possible by sharp dissection, damage of organs is hardly preventable |

Table adapted from original publication: Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir, 1990: p. 1009-16

Adhesions develop in 89 – 93% of patients undergoing open abdominal or pelvic surgery.[6,7] Incidence rates of adhesion formation are lower after minimally invasive surgery, 45 – 62%.[7,8] Adhesions can also develop after other causes of peritoneal trauma, such as inflammatory conditions or radiotherapy.[2] The occurrence of adhesions does not only cause a lifelong risk of adhesive small bowel obstruction (ASBO). Other clinical consequences of adhesions are difficulties during reoperation, female infertility, and chronic visceral pain;

making it the most common cause of long-term complications in peritoneal surgery.[1] The incidence of ASBO is 2–3% in the first years after surgery in all patients who undergo abdominal or pelvic surgery.[1] The risk of ASBO depends on the anatomical location of surgery and the extent of surgery and peritoneal injury.[1–10] ASBO risk varies from 0.5% in abdominal wall surgery, 1.2% after upper gastrointestinal tract surgery to 3.2% in lower gastro-intestinal tract surgery and 4.2% in pediatric surgery.[1]

# PERITONEAL ADHESION INDEX:




| Regions: | Adhesion grade: | Adhesion grade score: |
|---|---|---|
| **A** Right upper | ____ | **0** No adhesions |
| **B** Epigastrium | ____ | **1** Filmy adhesions, blunt dissection |
| **C** Left upper | ____ | **2** Strong adhesions, sharp dissection |
| **D** Left flank | ____ | **3** Very strong vascularized adhesions, sharp |
| **E** Left lower | ____ | dissection, damage hardly preventable |
| **F** Pelvis | ____ | |
| **G** Right lower | ____ | |
| **H** Right flank | ____ | |
| **I** Central | ____ | |
| **L** Bowel to bowel | ____ | |

**PAI** ☐

**Figure 1** Peritoneal Adhesion Index (PAI)

Given the high incidence of adhesions and adhesion-related complications, one would assume that every surgeon is aware of the risks of adhesions. However, awareness on the full size of the problem only arose in response to the publication of the Surgical and Clinical Adhesion Research (SCAR) study two decades ago. The SCAR large population based study demonstrated that one of three patients undergoing abdominal surgery is readmitted for a cause possibly related to adhesions.[11] Subsequently adhesion-related complications gained increasing awareness of clinicians, hospitals and vendors, and adhesion reduction strategies were introduced. Laparoscopic surgeons hypothesized that minimally invasive surgical techniques would reduce peritoneal injury and thereby could solve the problem of adhesion formation. Other strategies to reduce adhesion formation were the development of adhesion barriers, the banishment of powdered gloves, and the introduction of new sealing devices.[12]

Over the past decades, minimally invasive surgery has become the standard approach in many surgical disciplines. The rapid introduction of minimally invasive surgery was largely fueled by short-term benefits such as quicker recovery, reduced pain, and better cosmetic outcome.[13] Furthermore, surgeons strongly believed in the effectiveness of minimally invasive surgical techniques to reduce adhesion formation and subsequent morbidity.[14] For this reasons adhesion barriers are only seldomly used in minimally invasive surgery[15], and are believed to be needed only in open surgery. Despite good evidence of effective reduction of adhesion formation and subsequent adhesion-related morbidity, the use of adhesion barriers in open surgery is also limited.[16] Reasons for not using adhesion barriers are the lack of trust in adhesion reduction, the expected limited impact on adhesion-related complications, and the costs of the barriers.[15] The limited use of adhesion barriers has slowed down the research and development of adhesion-prevention strategies in the past decade.

Studies on adhesion formation in minimally invasive surgery report a reduction of approximately 50% in the extent of postoperative adhesions compared with open surgery.[7] Unfortunately, trials comparing open and minimally invasive surgery have not been designed and powered to compare long-term adhesion-related outcomes.[17] Therefore, the effect of the broad implementation of minimally invasive surgery on clinically relevant

outcome parameters such as ASBO and readmissions is unknown.[17] A reduction in adhesion formation, does not necessarily correlate with a proportionate reduction in the risk of ASBO; a single adhesive band may cause a life-threatening bowel obstruction, whereas extensive dense abdominal adhesions may be asymptomatic.[18] Nevertheless, potential benefits of minimally invasive surgery in preventing adhesion-related morbidity seem compelling.

Minimally invasive surgery may also play a role in the treatment of ASBO. Approximately 25% of patients with ASBO require surgery to resolve the bowel obstruction[1], and recurrence rates are high.[19] The minimally invasive approach is hypothesized to accelerate recovery, and might also reduce risk of regrowth of adhesions and subsequent recurrence of ASBO. A caveat is the small working space and vulnerability of the bowel caused by the distention of the obstructed bowel that could result in iatrogenic injuries. In this chapter, we discuss recent evidence on the effects of the introduction of minimally invasive surgery on the burden of adhesions and ASBO. We further discuss the role of minimally invasive surgery in the treatment of patients with ASBO. We end with a contemplation on the awareness of adhesion-related complications and the value of adhesion barriers in minimally invasive surgery.

**2. The problem of adhesive small bowel obstruction**

The vast majority of adhesions develop after abdominal or pelvic surgery, although adhesions can also form after abdominal and pelvic radiation and peritoneal inflammation.[2] Adhesions are associated with a lifelong risk of ASBO. Incidence and morbidity of ASBO might be somewhat difficult to estimate and compare between studies based on different definitions for ASBO. Most accepted definition of ASBO is an episode of SBO with the presence of adhesions confirmed during reoperation. However, operative confirmation of adhesions is often not possible because many ASBO episodes are managed non-operatively. Therefore a second definition of ASBO is commonly applied: an episode of SBO interpreted as matching ASBO on radiological imaging after excluding other potential causes of bowel obstruction e.g. hernia, tumor, bezoar.

In a systematic review, the incidence of SBO by any cause after surgery is estimated 9%.[1] In 42 etiological studies on SBO, adhesions accounted for 56% of all SBO episodes, either by operative confirmation or by excluding all other potential causes of SBO.[1] The incidence of postoperative ASBO confirmed by surgery is estimated at 2.4%. Depending on the type of initial surgical procedure, the incidence varied between 0.5 and 4.2%.[1] As mentioned, this estimate is conservative because most episodes of ASBO are managed non-operative.

Another way to estimate the burden of ASBO is based on population studies. In the SCAR study more than one in three patients were readmitted for a cause possibly related to adhesions, and more than 1 in 20 patients (6%) who underwent open abdominal or pelvic surgery were readmitted for a directly adhesion-related cause.[11] The most common diagnosis for a directly adhesion-related readmission was ASBO.[11] More recent population studies in the UK and USA show that ASBO remains a major contributor to the morbidity, mortality and costs related to emergency abdominal surgery. In the UK in 2016, 51% of all emergency laparotomies were for ASBO.[20] Similar results were found in the USA between 2008 and 2011, where SBO needing adhesiolysis belonged to the top 5 of emergency surgical procedures.[21] Given these numbers and the number of patients undergoing abdominal or pelvic surgery, the impact of ASBO on a population level is high.

ASBO causes significant morbidity and a hospital admission for SBO is associated with 2.5% mortality.[1] Initial non-operative management of ASBO includes gastric decompression, fluid resuscitation and nil per os, which is successful in 70–90%.[1–23] In a sizable number of cases ASBO will result in emergency or delayed, after failed initial conservative management, abdominal surgery. Open or minimally invasive adhesiolysis to resolve the obstruction is associated with an incidence of 6–20% enterotomies.[24,25] In general, complex adhesiolysis is associated with bleeding, sepsis, wound infections and increased mortality, even in the absence of bowel injury.[26] Mean length of hospital stay for ASBO ranges from 4 to 13 days and generally depends the type of treatment and the treatment complications.[1]

Both operative and conservative management of ASBO are associated with a risk of recurrent ASBO. Operative management includes repeated peritoneal injury with risk of adhesion reformation and re-ASBO. Non-operative management of ASBO does not dissolve

abdominal adhesions and harbors the risk of a new episode of ASBO. In a recent study of patients presenting with a first episode of ASBO, operative management was associated with a lower risk of recurrence compared with non-operative management (13% vs. 21%) after a median follow-up of 3.6 years.[19] The study also showed an increased risk of ASBO with every previous episode of ASBO in accordance to findings done 25 years ago.[27] Also the time between episodes of ASBO decreases with an increase in number of episodes.[19] Despite the higher recurrence rate after conservative treatment, current guidelines still recommend a trial of non-operative management of ASBO in order to avoid the risk of complications associated with surgical intervention.[28]

Effort is made to predict the severity of ASBO using peri-operative scores.[29,30] However, the scores are not widely adopted for clinical use. The American Association for the Surgery of Trauma (AAST) developed a score based on clinical, imaging, operative and pathologic criteria to grade disease severity of ASBO.[31,32] The AAST grade uses clinical criteria (flatus, bowel sounds abdominal distention), pathologic criteria (bowel perforation), imaging criteria on CT (intestinal distention, transition point, contrast flow) and operative criteria (intestinal distention, impeding bowel compromise, peritonitis) to define the grade of ASBO on a scale from 1 to 4. A higher AAST score for emergency ASBO is associated with an increase in length of hospital stay, pneumonia, and more severe complications.[33] Recently the Clinical Adhesion Score (CLAS) was developed, measuring the full spectrum of the long-term burden of adhesion formation in post-operative patients. CLAS calculates the overall morbidity based on four domains: ASBO, difficulties during reoperation, female infertility or subfertility, and chronic abdominal pain (data not yet published). Evaluation of current and new adhesion prevention strategies regarding long-term clinical efficacy e.g. ASBO could benefit from using CLAS.

The economic burden of ASBO is high. Operative management is the single most important determinant of costs. However, based on fewer recurrences of ASBO after surgical treatment, surgery may save costs at the long term.[34] Several studies have been reported regarding the treatment costs of ASBO. Most have important limitations reporting part of the costs or costs based on reimbursement prices rather than true healthcare costs.[35–37] We modeled in a recent study, costs for ASBO in the Netherlands using a micro-costing method

including costs of length of stay, ICU days, operative time, medication, parenteral feeding, imaging studies and laboratory studies.[38] This modeling revealed total healthcare costs of patients operated for ASBO of €16305 (SD €2513) with a mean hospital stay of 16.0 ± 11 days. For non-operatively treated patients costs would be €2277 (SD €265) with a mean hospital stay of 4.0 ± 2.0 days. The majority of the costs were due to ward stay, operative time, ICU stay and (parental) feeding. All surgical procedures for ASBO in this study consisted of open adhesiolysis. Costs estimated in this study were higher compared with previous estimates of treatment costs for ASBO with comparable lengths of stay and, as a result of its design better reflecting reality.[35–37] In the study we adhered to international guidelines for the diagnosis and treatment of ASBO increasing generalizability of outcomes for developed countries. Nevertheless costs may vary among countries due to differences in admission and discharge policies, and prices of diagnostics, materials, medication and feeding.

**3. The impact of minimally invasive surgery on morbidity of ASBO**

It has been suggested from a few studies that the decreased adhesion formation after minimally invasive surgery associates with a lower incidence of ASBO. This decrease seems limited compared with open surgery as concluded from one systematic review and one trial reported by our group.[1,17] Differences in definitions of ASBO used, types of procedures, outcome parameters and length of follow-up in the studies, preclude a firm conclusion on the beneficial effect of minimally invasive surgery on development of ASBO.

To estimate the impact of minimally invasive surgery at a population level on adhesion-related complications, ASBO in particular, our group recently reported the results of the SCAR update study.[39] Over 72,000 patients, who were operated between June 2009 and June 2011, were followed for a minimum of 5 years. Readmissions were classified, according to the initial SCAR study (1999), as directly-related to adhesions e.g. adhesive small bowel obstruction, possibly related to adhesions, e.g. any small bowel obstruction and reoperations potentially complicated by adhesions e.g. right hemicolectomy years after an appendectomy. Approximately 30% of all index procedures were minimally invasive.

Patients who underwent minimally invasive surgery were readmitted less frequently for directly related causes compared with patients after open surgery (1.7% vs. 4.3%). Possibly related readmissions and reoperations potentially complicated by adhesions were also less frequent (16.0% vs. 18.2% and 8.6% vs. 15.0%). Multivariate analysis revealed a 32% reduction in directly adhesion-related readmissions associated with minimally invasive surgery. Readmission rates were similar when comparing patients with open surgery in the SCAR and those in the SCAR update study. The overall small differences found in readmission rates could be explained by the difference in follow-up, 10 years in the SCAR study and 5 years in the SCAR update study. Despite the finding of a small reduction in readmission rates after initial minimally invasive surgery, the overall burden of adhesion-related readmissions on a population level remains high.

To further elaborate differences in adhesion-related readmissions between minimally invasive and open surgery, we analyzed patients with colorectal procedures (data not yet published). This type of surgery is known for its adhesion formation propensity and associated morbidity. Over 15,000 patients underwent colorectal surgery of whom almost one-third with a minimally invasive approach. For open colorectal surgery readmission rates were comparable between the SCAR study and the SCAR update study. Minimally invasive colonic and/or rectal surgery reduced the total number of directly adhesion-related readmissions. However in patients who underwent a (sub)total colectomy readmission rates were over 15% irrespective of an open or minimally invasive approach. Minimally invasive surgery did not reduce adhesion-related complications in rectal procedures. We concluded that an extended colectomy and rectal resection do not benefit from minimally invasive surgery regarding adhesion-related complications. We hypothesized that the large extent of the dissection and injury to the visceral and lateral parietal peritoneum needed in both surgical techniques abolishes the preventive effect of the minimally invasive technique on adhesion formation to the ventral peritoneum, where the injury is relatively limited for both approaches.

The SCAR update study has demonstrated that minimally invasive surgery is associated with less adhesion-related readmissions. Hence, the overall burden of adhesion-related readmissions on a population level remains high. Adhesion formation therefore continues

to be a challenge in abdominal surgery, also in the minimally invasive era. Minimally invasive procedures were only performed in approximately one-third of procedures in 2009 – 2011, whereas currently in the Netherlands about 75% of colonic resections are performed minimally invasive (by laparoscopy or robot).[40] On a population base a further decline in adhesion-related complications can be expected with an increase of minimally invasive abdominal operations. However, we like to warn against unbridled optimism regarding the overall impact of minimally invasive surgery on the burden of adhesions because open surgery is still being preferred when a complicated condition is expected in the abdominal cavity e.g. after multiple previous procedures, with large inflammatory mass or locally advanced cancer.[41] Many of these conditions are complex specifically due to presence of adhesions at baseline surgery and the need to perform adhesiolysis before entering the operative area. It is known that the propensity to reform adhesions after adhesiolysis is higher than de novo adhesion formation.

**4. Management of adhesive small bowel obstruction**

Adequate management of ASBO depends on an initially correct diagnosis. Although ASBO is a common diagnosis with clear signs and symptoms, misdiagnosis and delayed diagnosis are a substantial clinical problem. Up to 50% of older patients are initially not adequately diagnosed.[42] Failure to diagnose represents 70% of malpractice claims in ASBO.[43,44] In this regard it is important to note that patients with ASBO can initially present themselves to a variety of physicians, including general practitioners, surgeons, internal medicine physicians, geriatricians and gastroenterologists. To improve diagnosis of ASBO, multiple specialists need to be involved in practice guidelines and protocols. Based on expert opinion the diagnosing of ASBO includes a medical history with an assessment of potential causes of SBO, e.g. previous abdominal surgery, inflammatory bowel disease, important symptoms such as vomiting, absence of stools or flatus, intermittent colicky abdominal pain and abdominal distention. Common pitfalls in diagnosing ASBO are the less prominent pain present in the elderly[42], reporting of watery

diarrhea by patients with an incomplete obstruction and normal stool passage in the first days after onset due to stool still present in the colon.

The recent update of the international guideline for diagnosis and management of ASBO gives the current best available evidence for management of ASBO once the diagnosis of bowel obstruction has been established.[28] The first priority in management is to establish the cause of obstruction and to determine if urgent surgical treatment is required. ASBO is the single most common cause for SBO, the differential diagnosis includes strangulated abdominal wall or groin hernia, tumor, paralysis, constipation or bezoars. Laboratory tests should include blood count, CRP, electrolytes, creatinine and lactate. Imaging studies can include water-soluble contrast studies or computer tomography (CT) scans. CT scan is the preferred imaging technique for the diagnosis of ASBO, it can accurately rule out other causes of obstruction and identify patients who might require emergency surgery.[28] Water-soluble contrast enhances the diagnostic accuracy of CT scans. Signs that might suspect ASBO on imaging studies are an abrupt change in bowel diameter and the exclusion of other causes of SBO. The value of plain X-rays is limited.[28]

Urgent surgery is required in case of signs of ischemia, perforation or strangulation of the bowel, generalized peritonitis and/or hemodynamic instability. No single test is highly sensitive for ischemia and strangulation. Sensitivity of physical examination for the detection of strangulation is only 48% in experienced hands.[45] Laboratory tests indicating peritonitis or ischemia are a CRP above 75 and a white blood cell count above 10.000/mm3.[45–47] Again, a CT scan is most accurate in assessing strangulation and perforation and the need for emergency surgery.[28] CT abnormalities indicating strangulation or perforation are free intraperitoneal air or fluid, closed loop obstruction, mesenteric edema or engorgement, mesenteric swirling, pneumatosis intestinalis, decreased or lack of bowel enhancement or thickened bowel wall.[48–50]

If bowel obstruction is caused by adhesions, and signs of peritonitis, ischemia, and strangulation are absent, initial conservative treatment is reportedly safe. Conservative treatment is successful in 70 – 90% of all episodes of ASBO.[1,23] Conservative treatment of ASBO consists of nil per os and decompression of the gastro-intestinal tract using a naso-

gastric tube. Further management includes fluid resuscitation, correction of electrolyte disturbances, nutritional support and prevention of aspiration. Optimal duration of a conservative trial is debated; prolonged management for more than 72 h has been associated with adverse outcomes and increased mortality.[20,51–54] Water-soluble contrast studies seem useful in the follow-up of conservative management of ASBO. If contrast has not reached to colon 24–48 h following administration, continuation of conservative management is likely to fail and surgical management should be considered.[28] An algorithm for the diagnosis and treatment of ASBO is presented in Figure 2.[28]

*4.1 Role of minimally invasive surgery in the management of ASBO*

Operative treatment of ASBO historically comprises an explorative laparotomy with adhesiolysis. The increased use of minimally invasive surgery has raised the question whether minimally invasive surgery is feasible and effective for the treatment of ASBO. Benefits of minimally invasive adhesiolysis are reduction of peritoneal injury possibly resulting in less adhesion reformation, a quick recovery and minimal post-operative pain. Twenty-five years ago the first cases of minimally invasive surgery for treatment of ASBO have been described.[55] Thereafter a few series were reported but adequate comparative trials are scarce.[56–60] Minimally invasive surgery for ASBO is challenging because there is little laparoscopic working space due to the distended bowel. Also visibility can be hampered by multiple adhesions. There are concerns that minimally invasive surgery increases the risk of iatrogenic bowel perforations.[57] Suitability of minimally invasive surgery for ASBO further depends on patient characteristics. In case of hemodynamic instability open surgery is required because patients cannot tolerate the pneumoperitoneum.

One randomized trial comparing minimally invasive and open surgery for ASBO has been performed.[56] Only patients with a high suspicion of a single adhesive band causing the obstruction were included. Patients with confirmed or suspected peritoneal carcinosis, known multiple adhesions, previous open surgery for endometriosis, aorta, iliac vessels or Crohn's disease, previous generalized peritonitis, abdominal malignancy, previous abdominal radiotherapy or recent operations within 30 days were all excluded. Patients

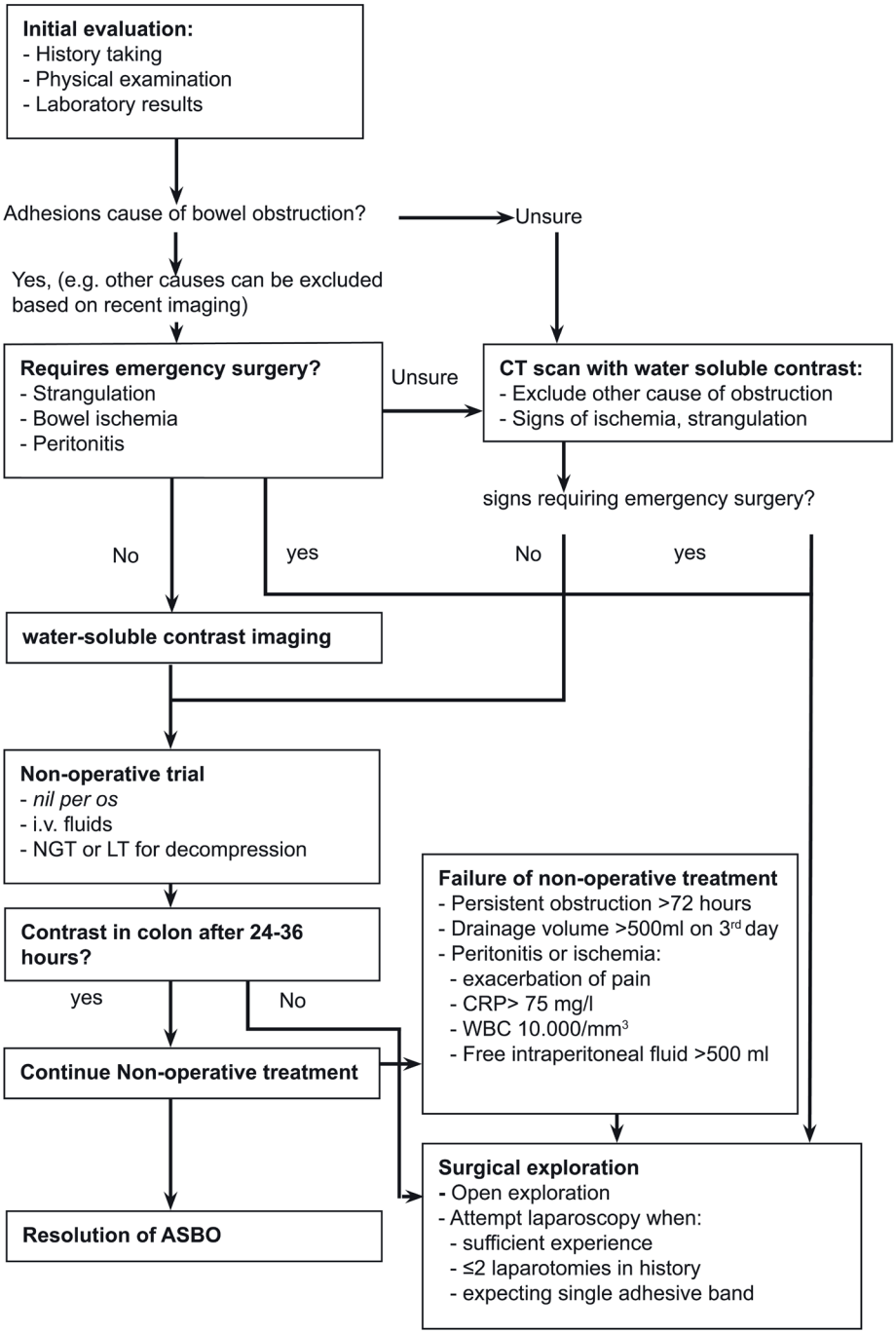



**Figure 2** Algorithm for the diagnosis and treatment of ASBO

started with conservative management of ASBO. If the obstruction did not resolve patients were randomized between open and laparoscopic adhesiolysis. The trial was open label, therefore patients and care providers were not blinded. During 5 years 566 patients were included in the study, 104 patients underwent surgery, 51 were randomly assigned to the open surgery group, and 53 to the laparoscopic surgery group. Patients in the laparoscopic group had a shorter length of stay (4.2 days) compared with the open group (5.5 days). Mortality and postoperative complications did not differ between the groups.

The few matched cohort studies comparing minimally invasive and open surgery for ASBO reported comparable results to those of the trial mentioned above.[59,60] There seems a trend towards a faster recovery in selected patients. Studies showed no major differences in complications or mortality. A few studies specifically addressed the potential drawbacks of the minimally invasive approach and suggested an increased risk of bowel injury.[59] Notably, the non-matched cohorts frequently claim large beneficial effects of the laparoscopic approach.[40,58] However, these studies have a high risk of various types of selection bias, mainly excluding patients who are more sick or are suspected of multiple adhesions.

It seems that minimally invasive adhesiolysis holds promise for patients with signs of a single adhesive band and an uncomplicated disease course. Further studies are needed to identify patients who can benefit from minimally invasive adhesiolysis and patients who can be harmed by minimally invasive treatment for ASBO.

## 5. Future perspectives

### *5.1 Awareness of adhesion formation by minimally invasive surgery*

Morbidity of adhesion formation in minimally invasive surgery is often underestimated. Less than 25% of surgeons and 5–83% of gynecologists routinely inform their patients about adhesions and the life term risk of adhesion-related complications.[14,62] However, recent evidence shows that adhesion-related morbidity remains high in the minimally invasive era.[39] Not informing patients about the risk of adhesions might therefore be considered

negligent. Increased awareness of adhesions might create an urge for the development and refinement of adhesion prevention strategies.

Awareness of adhesions may improve by growing awareness for intra-operative complications in general. Impact of adhesions on the operative course of reoperations for ASBO or other indications is often underreported. In a prospective comparison of operative notes and observation by an independent researcher, one in seven iatrogenic bowel injuries was not reported in operative notes, and almost one in three minor injuries.[63] In recent years, there is increasing scientific interest in the consequences of intra-operative events. IAEs are associated with 40% more hospital admissions, a twofold higher readmission rate, and with worse post-operative outcome.[64–70] Recently the Classification of Intraoperative Complications (CLASSIC) has been developed as a new tool for systematic classification for intra-operative complications (iAEs).[71] CLASSIC defines iAEs as any deviation from the ideal intraoperative course, including technical failures, surgical and anesthesiological difficulties. The score has been updated to five grades of severity (https://clinicaltrials.gov/ct2/show/NCT03009929). Lysis of adhesions at reoperations is associated with post-operative increase of sepsis, intra-abdominal complications, wound infections, longer hospital stay, and higher hospital costs.[26,72] As such, adhesiolysis qualifies as an iAE if adhesiolysis is not the intended surgical procedure. We currently investigate the contribution of adhesiolysis and associated intra-operative complications e.g. bleeding, inadvertent enterotomy, to CLASSIC.

Recent published guidelines may also increase awareness of adhesions and treatment of ASBO.[28] An old saying on ASBO is ‘you must not let the sun rise on ASBO’, all patients presenting with ASBO were operated if conservative management failed to resolve the bowel obstruction within 24 h. Recent insights report that a conservative trial can safely be prolonged to 72 h.[51,52] The current guideline states that conservative treatment should be instigated in all patients without signs of ischemia, perforation or strangulation of the bowel, generalized peritonitis and/or hemodynamic instability.[28] Contradictory, some studies report lower recurrence rates of ASBO after surgical management of ASBO.[19,27] A further disadvantage of prolonged conservative management is the further clinical deterioration of highly comorbid patients who receive starvation treatment for a few days.[73]

Minimally invasive surgery could change the paradigm again towards earlier surgical intervention because of faster recovery, reduced length of hospital stay and the mentioned lower recurrence rates of ASBO.

*5.2 Adhesion reduction strategies*

Considering the high impact of adhesion-related complications on a population level that is not substantially decreased by minimally invasive surgery, there is a pressing need to develop new adhesion reduction strategies.

Until now the most promising approach for reduction of adhesion formation is routinely applying an adhesion barrier. Adhesion barriers are bioresorbable liquids, gels or films that keep injured peritoneal wound surfaces separated. During separation the peritoneal wound can heal with restoration of peritoneal tissue morphology and function without 'scarring' (adhesions). A large systematic review and meta-analysis in 2014 of 28 trials (n = 5191) showed benefits of several adhesion barriers in predominantly open abdominal surgery.[16] However, adhesion barriers are seldomly applied in abdominal or pelvic surgery.[14] Only 1 in 7 surgeons ever uses adhesion barriers.[14] Reluctance of surgeons to use adhesions barriers seems caused by doubts about cost-effectiveness and the need and possibility of adhesion prevention in minimally invasive surgery.

Cost-effectiveness of adhesion prevention in minimally invasive surgery is an important perquisite for implementation in every day practice. We performed a modeling study on cost-effectiveness of adhesion barriers in minimally invasive procedures with a high risk of adhesion formation.[74] Two strategies were compared: current clinical practice (colorectal surgery without the use of an adhesion barrier) and colorectal surgery with the use of an adhesion barrier (hyaluronate carboxymethylcellulose). Whilst hyaluronate carboxymethylcellulose as such is not applicable in minimally invasive surgery and a gel form has not properly been studied in minimally invasive surgery, probabilities were extrapolated from data of open colorectal surgery. Probability estimates were derived from literature. Costs of treatment of ASBO were derived from our previous report.[38] Cost of hyaluronate carboxymethylcellulose was estimated on $630, based on the mean number of films using an adhesion barrier was more effective than not using a barrier in minimally

invasive surgery, but it was more expensive. However, mean expected direct healthcare costs in the 4 years following index surgery increased with only $163 per patient. Cost estimates in this modeling study only included direct health care costs. Societal costs (e.g. absence from work) were not modeled in this study. Therefore an increase of $163 in direct health care may be neglectable considering potential gain in societal costs. Further research is needed on long term savings regarding socioeconomic costs with adhesion barriers also including the new SCAR update data of minimally invasive surgery.

An important limitation of most barriers is the inability to properly use these in minimally invasive surgery. Most barriers were developed more than two to three decades ago and were films intended for use in open surgery. This limitation and the disregard needing barriers in minimally invasive surgery have impeded implementation and continued research and development of barriers suitable for minimally invasive surgery (and open surgery). Recently some new barriers have been developed suitable for minimally invasive surgery. Studies on these new barriers are performed mostly in gynecologic populations, and show effectiveness reducing adhesions.[76,77] The important next step in adhesion prevention is the development of a new generation of barriers suitable for minimally invasive use in general surgery.[78,79] Using increased knowledge of the pathophysiology of adhesions, new barriers consist of bioactive and targeted technology e.g. modulation of inflammation.[2] Pilpel and colleagues developed a liquid solution modulating the fibrin matrix which is generated by the hemostatic system after peritoneal injury.[80] This novel therapy is currently tested in animal models. Robertson and colleagues are testing a drug (L-Alanyl-L-Glutamine) to regulate the formation of adhesions due to hypoxia and oxidative stress caused by surgical injury of the vascular supply to the tissue caused by surgical intervention.[81] The first results of this drug in a double-blinded placebo controlled study show that L-Alanyl-L-Glutamine is safe to use and is effective at reducing adhesion formation after laparoscopic myomectomies.[82] Definitive results from this study are expected in due time. When proven safe, effective and affordable in patients, these new bioactive and targeted technology agents should be administered during index minimally invasive surgery to break the sequence of intra- and postoperative adhesion-(re)formation related complications.

## 6. Conclusions

Adhesion-related morbidity remains a clinically relevant problem in the minimally invasive era. Minimally invasive surgery is associated with only a modest reduction in adhesion-related readmissions and incidence of ASBO. The growing body of scientific evidence provides the clinician with a firm guideline for the diagnosis and treatment of ASBO. Minimally invasive surgery in the management of ASBO appears to be safe and effective alternative to open adhesiolysis, however in a very selected patient group. To allow as many patients as possible to benefit from a minimally invasive approach future research should focus on the selection criteria for minimally invasive surgery in ASBO. Adhesion-related morbidity is often underestimated and complications of adhesiolysis underreported. Raising awareness of adhesions therefore remains important. Using newly proposed scores for intraoperative complications, may increase awareness for the intra-operative events caused by adhesions. Adhesion barriers can safely reduce adhesion formation, are cost-effective in open colorectal surgery and effective with slightly higher costs in minimally invasive surgery. Future research should focus on new bioactive barriers that are easily applicable in minimally invasive abdominal surgery and safe to use. Preventing adhesions during first minimally invasive surgery is key to break the sequence of intra- and postoperative adhesion (re)formation related complications.

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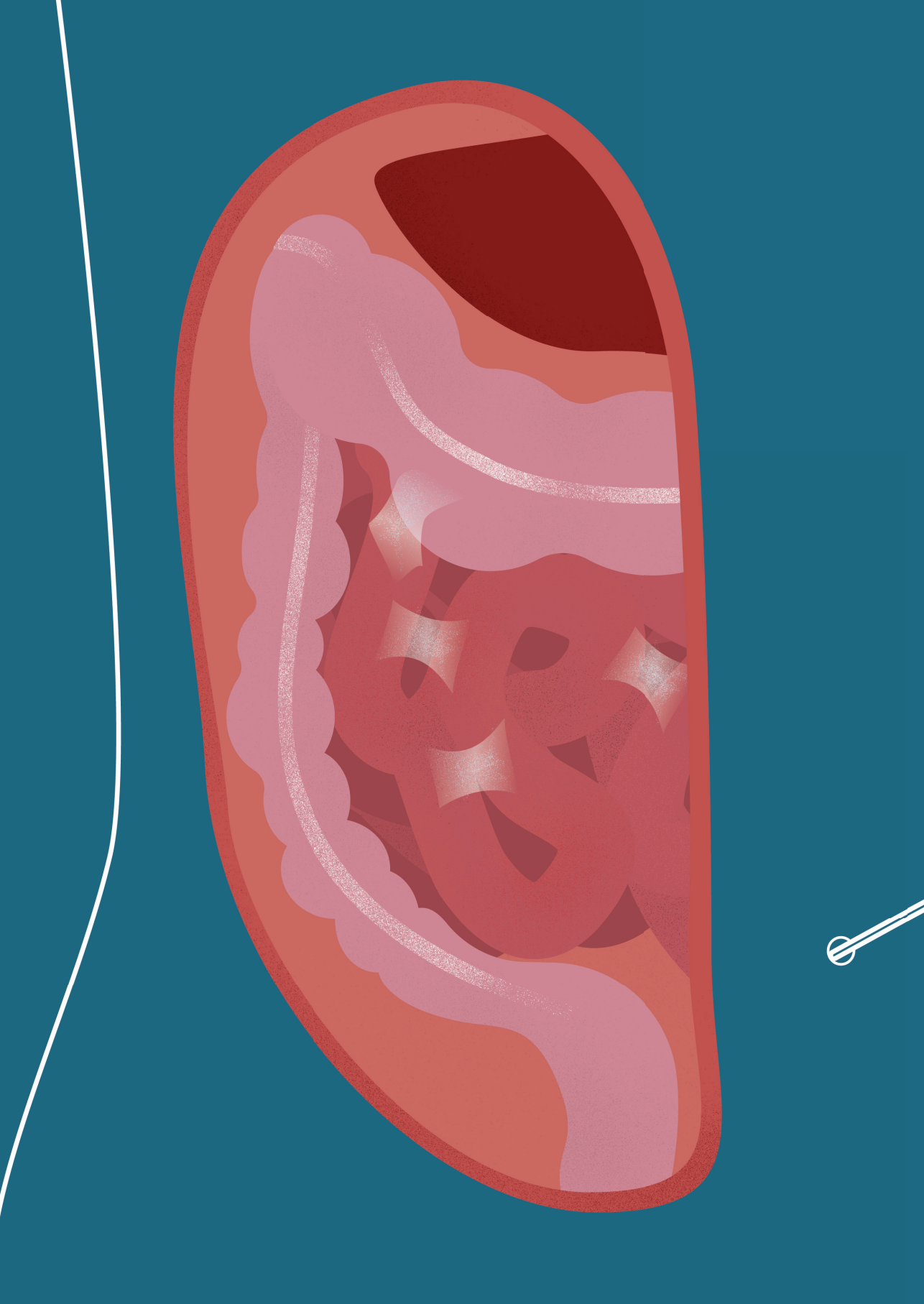
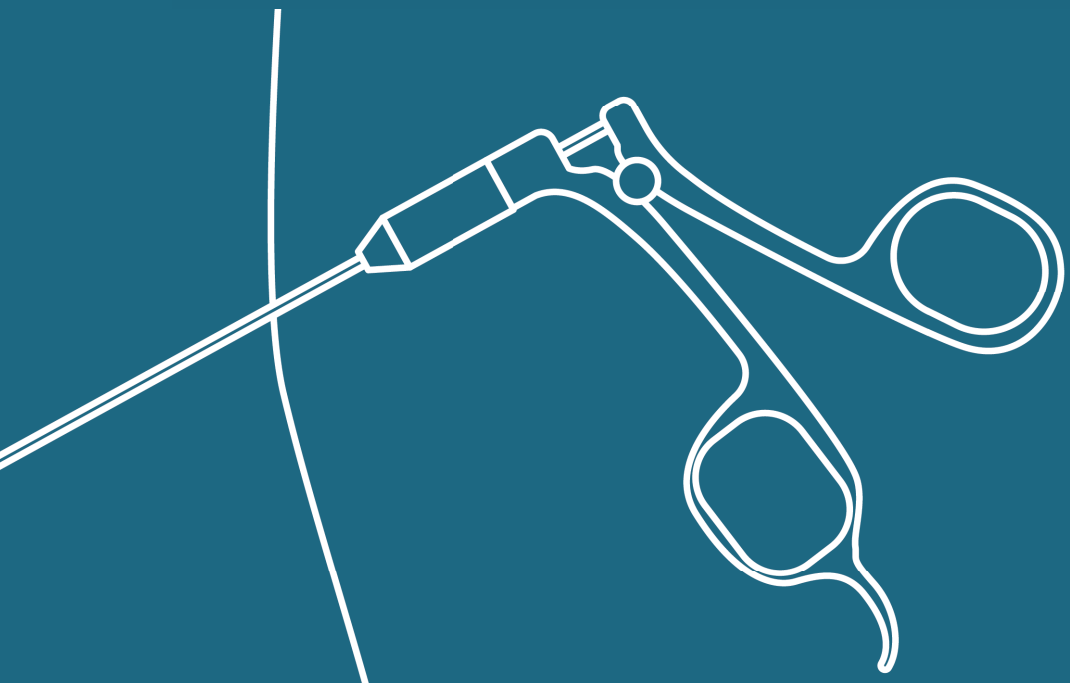


# 10

# Summary and future perspectives



**Summary**

For many years, minimally invasive surgery was believed to offer the solution for post-operative adhesion formation and associated complications.[1,2] Widespread confidence in the tissue-sparing effect of laparoscopy, combined with the limitations of first-generation adhesion barriers, has almost entirely halted further research into adhesion prevention in minimally invasive surgery.[3,4] This thesis aimed to determine whether laparoscopic surgery indeed has solved the "adhesion problem". To this aim, it was important to determine whether the clinical burden of post-operative adhesions has, in fact, decreased with the rise of laparoscopic surgical interventions for upper gastro-intestinal, hepato-biliary-pancreatic, colorectal, urological and gynecological diseases.

**Chapter 2** provides evidence from a large registry study demonstrating that while minimally invasive surgery in the abdominal and pelvic cavity is indeed associated with a reduction in adhesion-related complications, post-operative adhesions nonetheless continue to represent a significant driver of morbidity. In the five years following minimally invasive surgery, one in seven patients was readmitted for a cause possibly related to adhesions.[5] A substantial proportion of the readmissions were for adhesive small bowel obstruction (ASBO).

In **Chapter 3**, the impact of laparoscopy on adhesion-related complications was evaluated for colorectal surgery in particular. Colorectal surgery is notorious for bearing a high risk of adhesion-related complications; since laparoscopic colorectal surgery has become the standard treatment in many developed countries, it would be expected that this transition away from open surgery would have a substantial beneficial impact on the incidence of readmissions related to adhesion formation.[6,7] After laparoscopic colorectal surgery, we observe that 2.4% of patients were readmitted within five years for reasons directly related to adhesions, compared with 7.5% in open colorectal surgery. This difference was smaller for patients who had undergone rectal surgery, a group of patients with an almost twofold higher readmission rate compared to colonic surgery.[8] When outcomes were compared with those of the original colorectal SCAR study by Parker et al. in 2004, readmission rates for directly adhesion-related complications in open colorectal surgery tended to be higher,

4.8% vs. 7.5%. Changes of incidences of complications over time could not be reliably be attributed to the advent of laparoscopic colorectal surgery due to the limited availability of major laparoscopic surgery in the initial SCAR study.

ASBO is a frequent post-operative complication, even after minimally invasive surgery. However, there is a paucity of high-quality evidence regarding optimal treatment for ASBO. In **Chapter 4**, an updated guideline for the diagnosis and management of patients with ASBO is presented.[9] Indications for conservative and operative management of ASBO have shifted. Previous guidelines recommended operative treatment when symptoms did not subside within 24 hours after initiating optimal non-operative treatment. The guideline for ASBO now states that a non-operative trial for ASBO is safe to continue for 72 hours in the absence of signs of ischemia. CT scans should be performed in the diagnostic work-up given their 90% accuracy in predicting the need for acute surgical intervention.[10-12] When operative treatment is indicated, a minimally invasive approach may be beneficial. It should be noted that the latter recommendation was not based on conclusive evidence, as studies to date concerning laparoscopic adhesiolysis for ASBO have been small and potential prone to several biases.

In **Chapter 5**, the role of minimally invasive surgery was delineated for operative treatment of patients with ASBO, including the first randomized controlled trial (RCT) on this topic.[13] Minimally invasive surgery hypothetically reduces the peritoneal wound surface area, resulting in less adhesion reformation, less pain, and faster recovery. However, concerns were raised that laparoscopic treatment of ASBO would result in more harm than benefit, especially considering the potentially higher risk of iatrogenic bowel injuries compared with open procedures.[14] In this chapter, all papers regarding minimally invasive surgery were reviewed, and a meta-analysis was conducted. Results of this analysis showed that a minimally invasive approach is non-inferior to an open approach, but only when strict patient selection criteria are applied.

Abdominal reoperations, including for ASBO, are often complicated by severe and dense adhesions. Previous studies reported an increase in post-operative complications including mortality, sepsis and bleeding when complex adhesiolysis was necessary.[15] However, many

surgeons still have doubts about the extent of the clinical consequences of adhesions caused by abdominal/pelvic surgery, resulting in widespread neglect of the potential of adhesion reduction strategies. Awareness of the intra-operative consequences of adhesions would benefit from a broadly accepted and validated score on intra-operative adverse events, which would have a predictive value for post-operative complications. A new score for intra-operative adverse events, ClassIntra®, was previously developed and validated in a multicenter study, in which the Radboud University Medical Center was a participant.[16] However, specific variants of intra-operative adverse events, including adhesiolysis-associated bowel injuries, were not captured in this "all types of surgery" validation study. Furthermore, the inter-rater agreement was performed on vignettes and not real cases. In **Chapter 6**, a good inter-rater agreement of ClassIntra® was found for a well-defined cohort of elective abdominal operations with and without adhesiolysis. Adhesiolysis was one of the two strongest predictors of post-operative complications (OR 6.17; 95%CI 2.91 – 9.44). This confirmation of the association between intra-operative adverse events due to adhesiolysis and post-operative complications has direct implications for post-operative care, and should serve to increase awareness of adhesion-related morbidity and adhesion prevention.

Given the high incidence of adhesion-related post-operative complications, the financial impact of adhesions on health care system is substantial. Previous cost estimates of admissions for ASBO are outdated and mostly based upon reimbursements.[17,18] **Chapter 7** provides accurate cost estimates for patients who are admitted with ASBO, using micro-costing methods. The mean hospital stay for an episode of ASBO with operative treatment was 16 days, compared with 4 days for non-operative treatment. The in-hospital expense for an episode of ASBO with an operation was €16.305, in contrast to €2.277 for an episode without surgery.[19] This chapter provides a reliable cost-estimate for a modeling study on the impact of preventing adhesion-related complications with routine use of adhesion barriers in colorectal surgery, presented in **Chapter 8**. The use of a barrier in minimally invasive surgery would effectively reduce adhesion-related complications such as ASBO and complications from reoperations, while incurring only marginally higher health care costs.[20] Societal costs for ASBO treatment were not modelled in this study, but these are reasonably

expected to be high. The slight increase in direct health care costs was considered to be neglectable compared to anticipated societal savings.

**Adhesions and ASBO when minimally invasive surgery is the standard of care**

While minimally invasive surgery does significantly reduce adhesion formation and adhesion-related complications, it does not completely prevent adhesion formation after abdominal surgery.[5,21] A key question is if this reduction in adhesion formation is sufficient to prevent early- and long-term adhesion-related complications. The development of a single adhesive band after laparoscopic surgery, for example, could theoretically be more dangerous than a larger peritoneal area of adhesions in its capacity to induce a life-threatening bowel obstruction. In contrast, during repeat surgery, a single adhesive band has a minimal risk of iatrogenic organ injury compared with dense and extensive adhesions. Thus, a reduction of adhesion formation may have different effects depending on the type of adhesion-related complication. A recent observational study from our research group examining patients who had liver surgery after either laparoscopic or open colorectal surgery showed that adhesions to the ventral abdominal wall were significantly lower in the laparoscopic group compared with the open group, whereas adhesion formation in other areas of the peritoneal cavity were comparable.[21] It is plausible that the risk of ASBO over the course of a patient's lifetime will not decrease after minimally invasive surgery, but that the risk of an abdominal entry-related injury at repeat surgery will decrease after minimally invasive surgery. The dualistic effect of adhesion reduction was indirectly assessed in the SCAR update study by differentiating between readmissions directly (e.g. ASBO) and indirectly (e.g. reoperation) related to adhesions. However, this type of registry-based study, absent details on the disease and treatment characteristics, is not sufficient to answer the question of whether a reduction of adhesions is clinically relevant in the context of all adhesion-related early and long term complications. National cancer surgery registries generally collect more details on operative procedures and post-operative adverse events. However, these are also not suitable because follow-up data are limited and focus on cancer-related issues rather than complications due to adhesion formation.[22] New research

approaches using big data, artificial intelligence, and linkage of various databases are promising in their capacity to consider more detailed information on consequences of operations and risks for an individual level.[23,24] Intelligent analyses of existing databases could obviate the need for starting a laborious and expensive registry for adhesion formation and related complications in minimally invasive surgery.

Despite uncertainty regarding the benefits of minimally invasive surgery, we expect that incidences of adhesion-related complications will further decline in immediate future. Support for this expectation lies in the increased use of laparoscopy in major abdominal and pelvic procedures, surgeons' improved skill of surgeons, refinement of minimally invasive operative techniques and equipment, and around-the-clock availability of laparoscopic services for abdominal emergencies such as ASBO in many institutions. Nevertheless, adhesions and ASBO will remain as some of the most substantial problems after minimally invasive surgery. Incidences of anastomotic leakage (4-20%)[25,26] and incisional hernias (1-26%)[27,28] are similar or only moderately higher than those of ASBO[5], albeit with differing follow-up times.

Current international guidelines concerning the diagnosis and treatment of ASBO do not reflect the rise of minimally invasive surgery, and contain several recommendations that no longer comport with optimal management.[29] Unfortunately, the latest systematic review of the literature reporting a benefit of minimal invasive surgery in the treatment of ASBO reached its conclusions on the basis of suboptimal evidence.[13] Chiefly, this evidence was subject to reporting biases, with studies only examining "easy" cases of ASBO successfully treated by laparoscopic adhesiolysis. Substantial practice variations in the diagnosis and treatment of ASBO also make it difficult to draw conclusions on the optimal role of minimally invasive surgery in ASBO. Protocols and practices vary between countries, hospitals, and even individual doctors.

Patients with ASBO initially present to a variety of doctors including surgeons, gastro-enterologists, internists, geriatricians, and general practitioners. Initial and operative management often depend on the knowledge and skill of the consulting doctor and his/her perspective of the disease in the context of a given patient. For example, SBO after major

abdominal cancer surgery in an older person may be managed very differently by a medical oncologist and geriatrician versus an experienced surgeon; the latter may be more likely to take into account the 12-50 percent chance that the SBO is caused by adhesions and not by cancer recurrence.[30-34]

Our research group is currently performing a nationwide snapshot study on the management of ASBO in The Netherlands to determine practice variations in diagnosis, treatment, and associated outcomes, including the harms and benefits of laparoscopic adhesiolysis. Results from the study are anticipated to be finalized by late 2021, and could identify areas for future research. For example, we anticipate this work will clarify best practices regarding intra-professional collaboration for diagnosis and triage to intensive care units, use of laparoscopic approaches versus open surgery, and adherence to existing guidelines of management of (A)SBO. While we expect to find the general advantages of a minimally invasive approach such as accelerated recovery time and reduced post-operative pain[35], the question of operative safety (e.g. iatrogenic bowel defects) remains to be answered, as well as whether we can preemptively identify patients at greatest risk for adhesion-related intra-operative adverse events.[14] We are additionally interested in examining if centers with significant experience in minimally invasive surgery tend to initiate operative treatment earlier than the 72 hour window recommended by the guidelines for non-operative trial.[9]

By design, this study will not provide reliable information tailored to the individual patient. Individualization would, for example, demand rigid profiling of a patient with ASBO with scoring of clinical signs, symptoms, and radiological findings. Such scoring would only be accepted when it is easy to apply, and when it is validated for the post-operative complications that impact relevant patient reported outcomes measures (PROMs). In this context we refer to the LASSO trial, where selection criteria were described to randomize for laparoscopic or open surgery relieving ASBO, such as abdominal surgical history limited to solely laparoscopies or a maximum of 3 laparotomies, adequate bowel decompression prior to surgery, no generalized peritonitis in medical history, and no hemodynamic instability.[36]

A shaky point in the decision-tree regarding operative treatment of ASBO is frequently in the interpretation of results from currently-available imaging modalities, particularly in cases of recurrent and intermittent ASBO in the absence of ischemic symptoms. In these conditions, the decision over whether or not operative treatment would benefit long-term outcomes is considered to be more complicated than with an initial first presentation of ASBO. Good visualization of adhesions and determination of their contribution to the (partial) bowel obstruction(s) would support such decision-making. A promising novel imaging technique to visualize adhesions is cine-MRI.[37-39] Cine-MRI uses motional slides to visualize sliding of organs; in case of adhesions there will be abnormal or absent visceral sliding of organs. This technique has proven to be beneficial in the decision regarding where to enter the abdominal cavity in case of a reoperation, and to interpret abdominal complaints such as those occurring after an incisional hernia repair with a mesh.[38,40] Our group has substantial experience employing cine-MRI in patients with chronic abdominal or pelvic pain to determine eligibility for adhesiolysis. A treatment strategy with cine-MRI, shared-decision making, and adhesiolysis with application of barriers in patients with chronic abdominal pain was demonstrated to enable successful selection of appropriate patients for elective adhesiolysis, resulting in long-term pain relief in 80% of patients.[41] Adhesions mapping with cine-MRI revealed reliable information about the localization and extent of adhesions, and in some cases areas of distended bowel were accurately visualized. The mapping was also used to support the decision of open abdominal entry and adhesiolysis versus laparoscopic adhesiolysis. The yield of the cine-MRI in patients with chronic pain is promising for operative decision making in patients with recurrent episodes of semi or acute ASBO. Additionally, with increasing availability of MRI around-the-clock in hospitals, cine-MRI could be researched for cases of an initial acute episode of ASBO, compared with other imaging modalities such as CT or ultrasound.

An important knowledge gap in ASBO handled by minimally invasive surgery is the occurrence of a recurrent episode of ASBO. Current data report a reduction in recurrent ASBO after operative treatment, which was primarily performed via open adhesiolysis. Five-year readmission rates were around 20 percent for patients who underwent non-operative management compared with about 15 percent for patients who had an operation.[42-44]

Although not reported, we expect that the 25 percent decrease in admission rates was achieved without the use of an adhesion barrier after adhesiolysis. From a biological standpoint, knowing that reformation of adhesions is more aggressive than initial adhesion formation, adhesion barriers could reasonably be expected to further lower the recurrence rate.[45-47] It is known from animal experiments that most current barriers have limited efficacy in reducing adhesion reformation.[48] Our unpublished data of an animal cecal abrasion-peritoneal side wall injury study, in which Hyalobarrier® was applied to prevent adhesion reformation, showed a 90 percent reduction of adhesions at the injured area. This finding is promising because Hyalobarrier® gel has been developed for minimally invasive surgery.

The first human data on ASBO recurrence rates after minimally invasive surgery are expected in three years when the follow-up from the first RCT on minimally invasive surgery and ASBO -the LASSO trial- is completed.[36] Unfortunately, this trial will not provide a complete answer to this topic, and not for all patients with ASBO, because inclusion criteria for laparoscopic adhesiolysis were rather strict. Only patients with a high likelihood of a single adhesive band were included, and the sample size of the study is relatively small. Although the LASSO trial will add some evidence on recurrent ASBO after minimally invasive surgery, further research will be needed. Such research should focus more on individual patient and disease characteristics predicting long term benefit of minimally invasive surgery regarding ASBO and other adhesion-related complications. Individual patient and disease characteristics may include the innate propensity to form peritoneal adhesions, the adhesiogenic nature of the disease in question, and peri-operative course of the prior surgeries.[49,50] Our research group is currently running a trial to specify genetic factors that are associated with adhesions in patients with chronic abdominal pain. (https://clinicaltrials.gov/ct2/show/NCT03938168)

**Adhesion prevention in the minimally invasive era**

Despite now widespread use of minimally invasive surgery, peritoneal adhesions will continue to form and affect many patients' lives, and the healthcare system write large. Therefore, the need for adequate adhesion reduction strategies has not subsided.

Two to three decades ago, adhesion barriers were marketed as the solution to adhesion formation. Most barriers at that time were bioresorbable membranes or films intended to separate injured peritoneal wound surfaces until healing after open surgery.[51] Despite evidence that these barriers are safe to use and effectively reduce adhesion formation, broad use in abdominal and pelvic surgical procedures was not achieved.[1,2,51] This may be due to doubts about barriers' effectiveness, poor handling capabilities of films in minimally invasive surgery, perceptions that barrier use in minimally invasive surgery would not add additional value given the relatively high costs of the barriers, and/or some of the comments made by surgeons and gynecologists.[1] Obviously, there is a need for new formulations of anti-adhesive agents such as gels and sprays that are more easy to handle in minimally invasive surgical settings.[15,52] These new agents should also demonstrate safety and efficacy in adhesion reformation, as two out of three abdominal operations are reoperations, including adhesiolysis for ASBO.[15] In animal and human studies, efficacy of barriers preventing reformation of adhesions is a neglected area of research, despite the critical need for barriers felt most by surgeons confronted with an adhesion-related complication or when performing adhesiolysis. Animal data suggest that adhesion reformation is more difficult to prevent than de novo adhesion formation, findings which must be taken into account when developing and testing new anti-adhesive agents.[48] Future clinical studies should encompass both patients with virgin abdomens and patients with a history of previous abdominal operations.

An almost-forgotten adhesion reduction strategy in minimal invasive surgery is peritoneal conditioning. The $CO_2$ pneumoperitoneum in minimally invasive surgery induces mesothelial cell hypoxemia, resulting in an inflammatory reaction and subsequent adhesion formation.[53] Nitrous oxide ($N_2O$) addition to $CO_2$ has been shown to result in decreased adhesion formation in a mouse model.[54] Full conditioning of the peritoneum, such as

addition of $N_2O$, cooling of the abdomen to 30°C, gentle tissue handling, aspiration of adhesiogenic factors (e.g. blood, remaining fibrin), and post-operative administration of dexamethasone has been shown to reduce adhesion formation in abdominal surgery.[47,55] Lowering the intra-abdominal pressure results in improved perfusion of the peritoneum and is hypothesized to result in peritoneal tissue hypoxemia; however, it has not been clinically proven to further reduce adhesion formation.[56] Although all these measures can be undertaken at very low costs with minimal negative consequences, preconditioning of the peritoneum has not become routine. It would be of interest to study combinations of peritoneal conditioning and barriers minimizing adhesion formation in minimal invasive surgery.

*Novel adhesion reduction strategies in minimally invasive surgery*

When new anti-adhesion strategies are developed, they should meet the requirements for use in minimally invasive surgery. Most important are: ease of handling through a trocar and with peritoneal gas insufflation, reduction of adhesion reformation as well as de novo adhesion formation, and manufacturing ability at relatively low costs. Improved understanding of the pathology of adhesions has paved the road for the development of bioactive substances interfering with the adhesion formation process.[57-59] Our group is engaged in two promising strategies: a solution modulating the fibrin matrix, and a drug regulating hypoxia and oxidative stress caused by surgical injury.[50,60] In the first strategy, a selection of coagulation enzymes are extracted from human blood plasma and, processed as a solution that is sprayable (Eiobio, EIO Biomedical, Nazareth, Israel).[50] The coagulation enzymes facilitate clotting at peritoneal wound surface sites and form thin fibrin fibers that are heavily crosslinked. The fibrin network that develops leaves less interval spaces for innate fibrin formation and adhesion forming cells to integrate, with the net result of 'normal' healing of the peritoneum. Endogenous plasminogen will eventually activate fibrinolysis and dissolve the fibrin matrix in due time.[50] The solution has proven to reduce adhesion formation in an animal study.[50] Results from this study and an ongoing clinical trial will be published shortly.

The second adhesion reduction strategy, L-Alanyl-L-Glutamine (Evitar®, Temple® Therapeutics, Geleen, The Netherlands), interferes with adhesiogenic processes on a cellular level, suppressing hypoxia-induced levels of factors that trigger the inflammatory cascade and induce tissue fibrosis. Upregulation of hypoxia-induced factors by surgical disruption of the vascular supply, result in lactate formation and induction of profibrotic effectors that promote fibrin deposition and neovascular growth. This drug has proven to reduce hypoxia-induced triggers in in-vitro experiments.[60] A proof-of-concept trial exploring safety and efficacy of this drug on post-operative adhesion formation after myomectomies also showed promising results (unpublished data).

*Always use an adhesion barrier?*

Results of our population-based and cost-modelling studies support routine use of an adhesion barrier during a first operation in the peritoneal cavity. Health-care providers and insurance companies should invest in the routine use of barriers anticipating an overall reduction in adhesion-related morbidity and associated costs. This reduction would not only include ASBO but also complications at reoperation, female sub- or infertility and chronic abdominal pain. Currently, however, the increase in-hospital expenses that are not reimbursed, discourages broad use. Clinicians and policymakers in these hospitals will need a methodology that specifies which patients would benefit the most from barrier use. Based on the data from the Scottish National Health Service our research group is currently developing a simple tool to predict the risk of reoperation based on specific patient and surgical parameters. This nomogram, when externally validated, will provide surgeons with an overview of the individual risk for resurgery or ASBO in the first, second or fifth year after index surgery. When the risk for repeat surgery or ASBO exceeds a certain level, the patient and surgeon may discuss the application of an adhesion barrier during index surgery. Cut-off scores for the use of an adhesion barrier have yet to be defined in cost-effectiveness studies based on this nomogram. Cost-effectiveness is positively affected by low costs of a barrier. In the modeling study presented in Chapter 8, variations in the costs of an adhesion barrier had the largest impact on their cost-effectiveness.[20] Thus, the starting point for the development and introduction of new adhesion reduction strategies must be manufacturing capability at low costs.

Concluding statements on anti-adhesive strategies in minimal invasive surgery are:

- Newly marketed adhesion reduction strategies should be easy to use in minimally invasive surgery, reduce adhesion reformation as well as de-novo adhesion formation, and be mass-manufacturable at relatively low costs.
- Furthering our understanding of the pathophysiology of adhesion formation is key for developing bioactive agents that reduce adhesion formation.
- Increased use of adhesion barriers in all abdominal and pelvic operations, both minimally invasive and open, is an important step forward in reducing long-term consequences of adhesions in surgical patients. A new validated nomogram can support surgeons in daily clinical care to identify patients who would benefit the most from adhesion reduction strategies.
- Combining adhesion reduction strategies, current and new, might offer the solution enabling adhesion free surgery.

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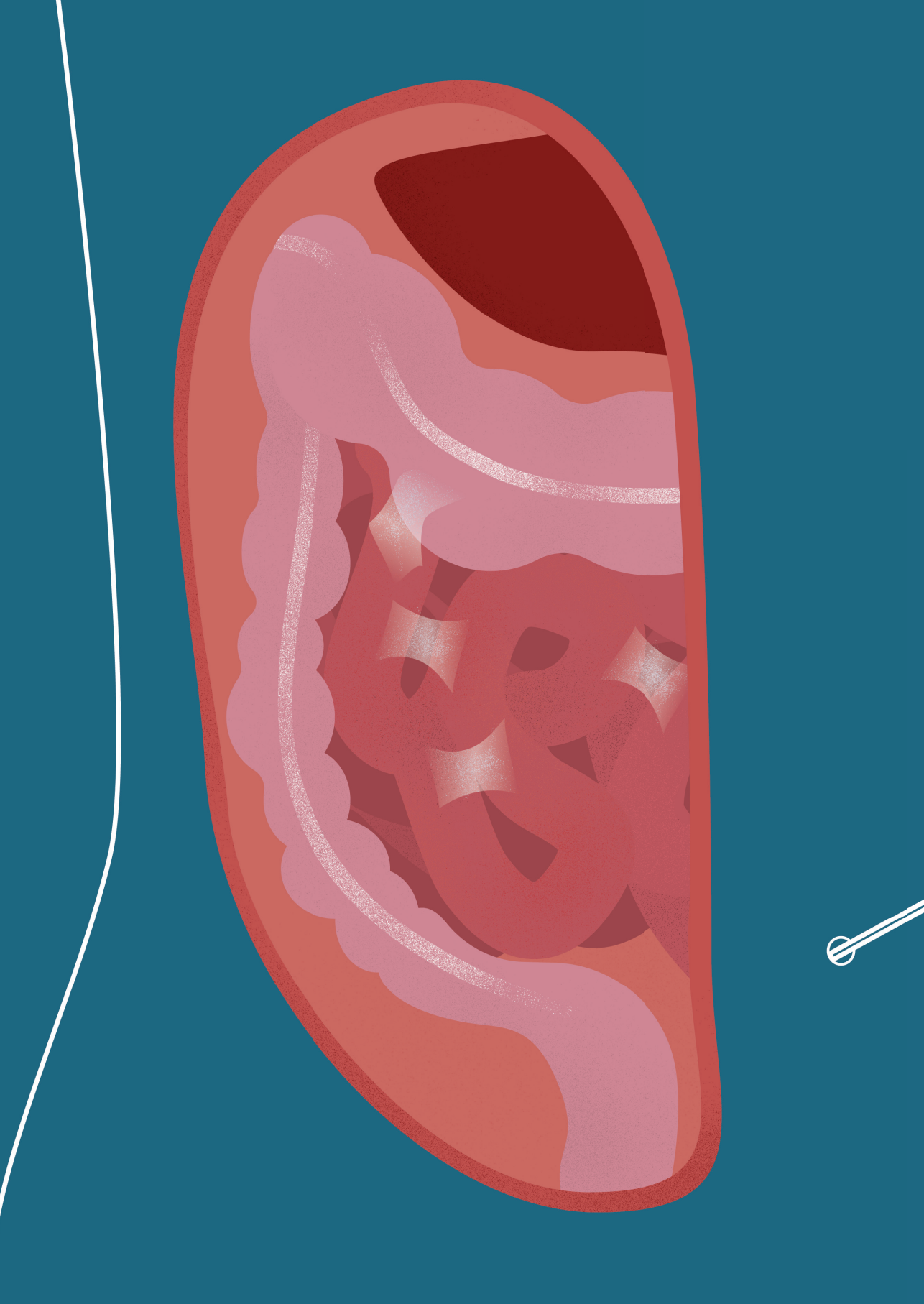
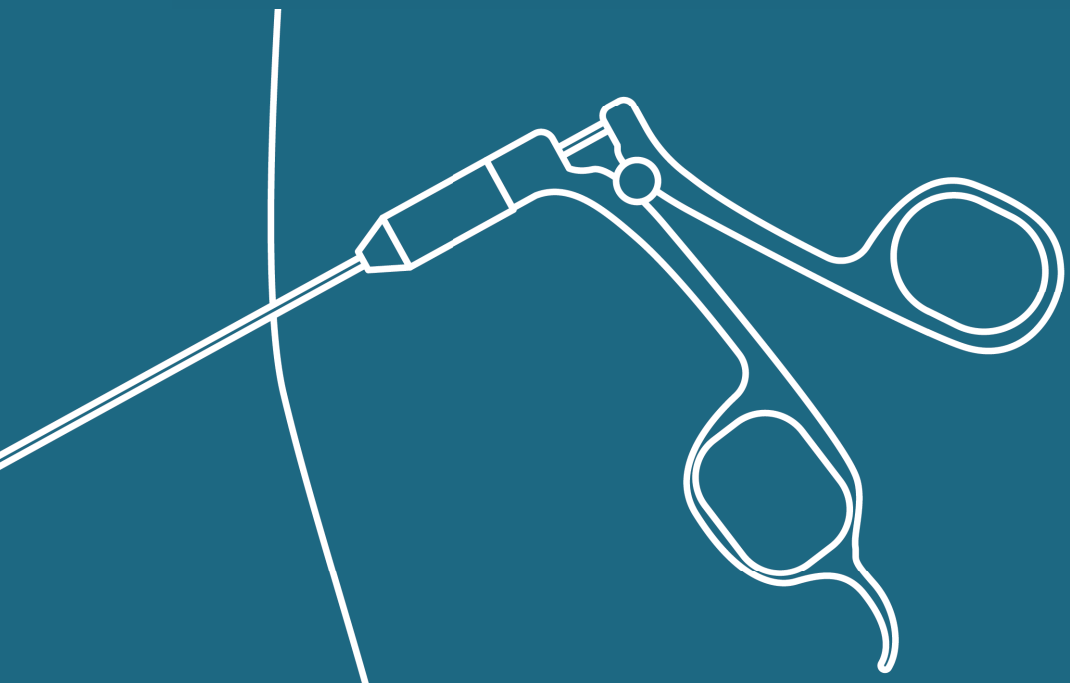


# Nederlandse samenvatting



Adhesies (verklevingen) ontstaan tussen organen en de buikwand als reactie op schade aan het peritoneum, het buikvlies dat alle buikorganen bedekt. De meest voorkomende oorzaak van schade aan het peritoneum is een operatie in de buik. Bijna alle patiënten die een open buik operatie ondergaan, ontwikkelen adhesies. Iets meer dan de helft van de patiënten die een kijkoperatie (laparoscopie) ondergaan ontwikkelen adhesies. Andere oorzaken van peritoneale schade zijn buikvliesontsteking, tumoren en radiotherapie. Adhesies geven een levenslang risico op dunne darmobstructies (strengileus). Daarnaast kunnen adhesies vrouwelijke onvruchtbaarheid, chronische pijnklachten en onbedoelde schade aan andere organen tijdens een volgende operatie veroorzaken. Het beperken van de schade aan het peritoneum door de minimaal invasieve eigenschappen van een laparoscopische operatie werd gezien als dé oplossing om adhesies en de mogelijke gevolgen daarvan te voorkomen. Het breed gedragen vertrouwen in laparoscopie als de oplossing voor adhesie-gerelateerde problemen en de beperkte effectiviteit en toepasbaarheid van beschikbare adhesie remmende middelen, heeft ervoor gezorgd dat adhesiepreventie in de afgelopen jaren weinig aandacht heeft gekregen. De belangrijkste groep van adhesie remmende middelen zijn de zogenoemde adhesiebarriers. Adhesiebarriers zijn middelen die na een operatie in de buik worden achtergelaten om wondoppervlakken van elkaar te scheiden, waardoor deze oppervlakken niet aan elkaar kunnen verkleven. De studies in dit proefschrift gaan over de vraag in hoeverre kijkoperaties het “adhesie probleem” hebben opgelost, en of er nog aanvullende maatregelen nodig zijn om de ziektelast van adhesies te verminderen. Om antwoord te krijgen op deze vraag hebben we onderzocht of het voorkomen van postoperatieve adhesie-gerelateerde complicaties is afgenomen met de toename van laparoscopische ingrepen. Samenvoeging van bewijs uit meerdere studies in een model geeft inzicht in de kosteneffectiviteit van adhesiebarriers in het voorkomen van adhesie-gerelateerde problemen na laparoscopie. Een andere studie verduidelijkt de rol van een laparoscopische ingreep in het voorkomen en behandelen van adhesie-gerelateerde problemen.

In **hoofdstuk 2** werd de invloed van een algemene toename van het aantal laparoscopische ingrepen onderzocht op het voorkomen van adhesie-gerelateerde problemen.

Hypothetisch zouden adhesie-gerelateerde problemen evenredig minder moeten zijn geworden met de toename van het aantal laparoscopische operaties. Hiervoor werd landelijke data gebruikt van de Scottish National Health Service (NHS). Alle patiënten die tussen 2009 en 2011 voor het eerst een buikoperatie ondergingen zijn geïncludeerd in deze studie. Op basis van diagnose- en operatiecodes werden heropnames die een relatie hadden met adhesies, gedurende vijf jaar geregistreerd, waaronder opnames voor strengileus. Heropnames werden onderverdeeld in de volgende drie categorieën: 1) zeker gerelateerd aan adhesies (bv. strengileus), 2) mogelijk gerelateerd aan adhesies en 3) heroperaties mogelijk gecompliceerd door adhesies.

Gedurende de studieperiode werden er 72.270 patiënten geopereerd, waarvan 30% laparoscopisch. Heropnames zeker gerelateerd aan adhesies kwamen minder vaak voor in de groep patiënten met een laparoscopische ingreep (1.7%) in vergelijking met de groep patiënten die een open operatie ondergingen (4.3%). Het risico op een zeker aan adhesie gerelateerde heropname was erg afhankelijk van het type operatie dat uitgevoerd was. Daarbij was het type operatie niet evenredig verdeeld tussen de open en de laparoscopische ingrepen. Na correctie voor het type operatie lag het aantal heropnames voor zeker aan adhesie-gerelateerde complicaties ongeveer 30% lager in de laparoscopiegroep. Het risico op een zeker aan adhesie-gerelateerde complicatie was het laagst bij patiënten die een verwijdering van de galblaas ondergingen, namelijk slechts 1%. Het risico was het hoogst na operaties aan de endeldarm (11%) en aan de dikke darm (10%). Veertig procent van alle zeker aan adhesie-gerelateerde heropnames was ten gevolge van strengileus. Er werd ook een afname gezien in het voorkomen van het aantal heropnames mogelijk gerelateerd aan adhesies (16.0% vs. 18.2%) en heroperaties mogelijk gecompliceerd door adhesies (8.6% vs. 15.0%). Deze studie bewijst dat adhesie-gerelateerde problematiek minder vaak voorkomt na laparoscopische ingrepen. Desalniettemin blijft de ziektelast van adhesies indrukwekkend, ook voor patiënten na een laparoscopische ingreep. Vervolgstappen zullen moeten worden ondernomen om de ziektelast van adhesies verder tegen te gaan. Veelbelovend hierin is de ontwikkeling van laparoscopische technieken om het peritoneale wondoppervlak nog verder te reduceren. Daarnaast komen er nieuwe adhesiebarriers beschikbaar, die effectief en gemakkelijk laparoscopisch toepasbaar zijn.

In **hoofdstuk 3** werd er specifiek gekeken naar de patiënten die een operatie aan de endel- of dikke darm hebben ondergaan in de studiepopulatie van hoofdstuk 2. Dikke- en endeldarm (colorectale) operaties staan bekend om het hoge risico op adhesieformatie en de daaraan gerelateerde complicaties. In de afgelopen twee decennia is een laparoscopische benadering de standaard geworden in colorectale chirurgie. Voor deze groep wordt dan ook de grootste en meest relevante daling in het voorkomen van adhesie-gerelateerde heropnames verwacht. Na een laparoscopisch uitgevoerde colorectale operatie werd 2.4% van de patiënten in de vijf jaar na operatie heropgenomen voor een zeker aan adhesies gerelateerd probleem, in de groep patiënten met open colorectale chirurgie was dit 7.5%. Het verschil tussen de open en laparoscopische groep was minder groot in de groep patiënten met een endeldarm operatie. Vergeleken met operaties aan de dikke darm werden deze patiënten twee keer vaker opgenomen voor zeker aan adhesie-gerelateerde problemen. Bij het vergelijken van deze resultaten met die van een eerdere studie met data van de NHS, viel op dat de incidentie van zeker aan adhesie-gerelateerde heropnames in de open colorectale chirurgie groep was toegenomen van 4.8% in de eerdere studie naar 7.5% in de huidige studie. Verschillen over tijd in het aantal heropnames in de laparoscopiegroep konden niet betrouwbaar worden bepaald, omdat het aantal laparoscopische operaties in de eerdere studie hiervoor te klein was. Het persisterende hoge risico op adhesie-gerelateerde complicaties in deze hoog risicogroep benadrukt de noodzaak voor de verdere (door)ontwikkeling van strategieën om adhesies te verminderen.

Een van de veelvoorkomende problemen van adhesies is strengileus, zelfs na een laparoscopische ingreep. Ondanks het vaak voorkomen van deze complicatie zijn er weinig studies van goede kwaliteit beschikbaar over de optimale behandeling voor strengileus. In **hoofdstuk 4** werd een bijgewerkte richtlijn gepresenteerd voor de optimale diagnostiek en behandeling van strengileus. In verschillende databases werd gezocht naar literatuur met betrekking tot de diagnostiek en behandeling van strengileus. Deze literatuur werd kritisch geanalyseerd en systematisch gepresenteerd in de bijgewerkte richtlijn.

De meeste gevallen van strengileus worden conservatief behandeld, dat wil zeggen zonder een operatie. De conservatieve behandeling bestaat uit ‘rust’ geven aan de darm, door niet te eten en te drinken en de druk op de darm te verminderen met een maagslang. Om

uitdroging te voorkomen, krijgen patiënten met een strengileus een infuus met vocht. In sommige gevallen is een operatie noodzakelijk om de adhesie(s) die de darm afknellen door te snijden of weg te nemen. De indicaties voor de conservatieve en operatieve behandeling van strengileus zijn veranderd in de loop der jaren. In voorgaande richtlijnen werd operatieve behandeling aangeraden indien er na 24 uur optimale conservatieve behandeling geen verlichting was van de symptomen. De nieuwe richtlijn stelt nu dat een conservatieve behandeling veilig kan worden gecontinueerd voor 72 uur, indien er geen tekenen zijn van een belemmering van de bloedtoevoer naar de darm. Een CT-scan wordt aanbevolen, omdat met deze beeldvorming goed kan worden voorspeld of acuut operatief ingrijpen noodzakelijk is. Wanneer er wordt besloten operatief te behandelen, lijkt een laparoscopische operatie enkele voordelen te bieden. De aanbeveling voor een laparoscopische benadering is echter niet gebaseerd op sterk wetenschappelijk bewijs, omdat de studiepopulaties klein waren en de relatief eenvoudige gevallen oververtegenwoordigd waren in de laparoscopiegroep.

In **hoofdstuk 5** is de rol van de laparoscopische benadering bij een strengileus verder onderzocht. Zoals eerder besproken is het peritoneale wondoppervlak kleiner na een laparoscopische operatie in vergelijking met een open operatie. Dit biedt het theoretisch voordeel dat er minder recidief adhesies ontstaan, dat er minder pijn is na de ingreep en dat de patiënt sneller herstelt. In eerdere publicaties werd echter bezorgdheid geuit over het feit dat het laparoscopisch opheffen van een strengileus, in vergelijking met open procedures, meer nadelen dan voordelen oplevert vanwege het grotere risico op onbedoeld darmletsel. In dit hoofdstuk werden alle artikelen over laparoscopische operaties voor een strengileus systematisch onderzocht, en werd er een meta-analyse uitgevoerd. Een beperking van deze systematische review en meta-analyse was dat veel studies retrospectief waren. Ook was er sprake van een forse selectiebias, want de groep patiënten die een laparoscopische ingreep had ondergaan, had vaker een ‘eenvoudige’ strengileus. Bij de moeilijke casus was, volgens geldende richtlijnen, meestal een open benadering toegepast. Vanwege deze selectiebias gaf vergelijking van deze twee groepen een mogelijk vertekend beeld van de resultaten ten faveure van de laparoscopiegroep. Om te voorkomen dat vertekening door selectie in de meta-analyse een rol zou spelen, werden alleen studies

waarbij vertekening door selectie onwaarschijnlijk was, meegenomen in de primaire analyse. Alle andere studies werden meegenomen in de sensitiviteitsanalyse. De resultaten van de primaire analyse lieten zien dat een laparoscopische behandeling van een strengileus even goede (en slechte) resultaten geeft als een open behandeling. In de sensitiviteitsanalyse leek een laparoscopische benadering een voordeel op te leveren; de postoperatieve sterfte was lager, de duur van de ziekenhuisopname korter, en er waren minder ongeplande heroperaties. Deze studie concludeert dat een laparoscopische benadering van strengileus niet onderdoet voor een open benadering, maar alleen bij een bepaalde, goed omschreven groep van patiënten.

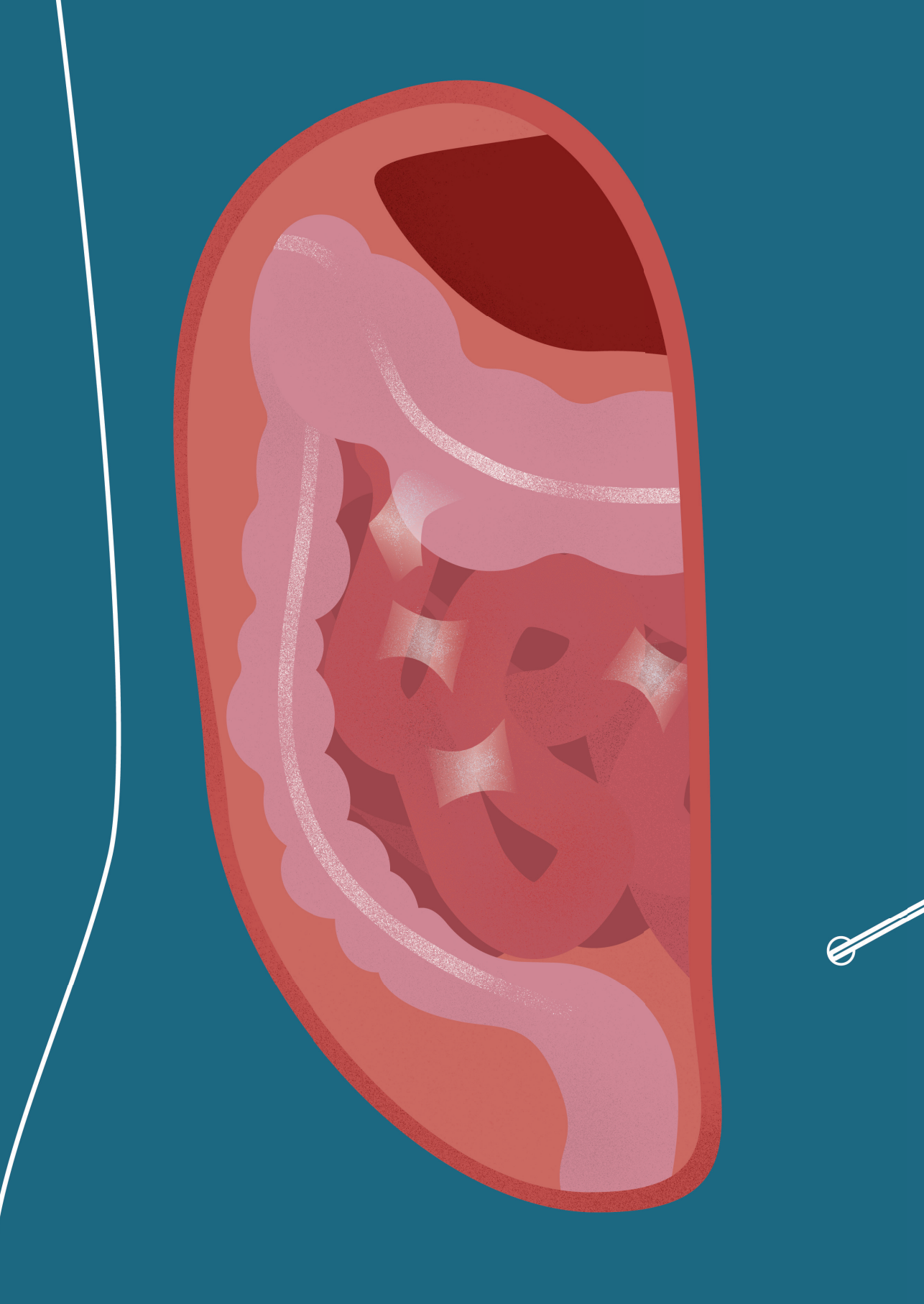
Heroperaties in de buik, onder andere voor strengileus, worden vaak gecompliceerd door uitgebreide en straffe adhesies. Eerdere studies rapporteren een toename van postoperatieve complicaties, waaronder overlijden, sepsis en bloeding wanneer een uitgebreide adhesiolyse (het losknippen van adhesies om toegang te krijgen tot het operatieterrein) noodzakelijk was. Veel chirurgen hebben echter nog steeds twijfels over de omvang van de adhesieproblemen, zeker na een laparoscopische operatie. Dit resulteert erin dat strategieën die adhesies kunnen voorkomen weinig worden toegepast. De bewustwording van de complicaties ten gevolge van adhesies bij heroperaties zou kunnen toenemen als de heroperaties beter en systematischer worden gedocumenteerd. Op deze manier kunnen complicaties die tijdens een operatie plaatsvinden ten gevolge van adhesiolyse worden gerelateerd aan complicaties die na de operatie optreden.

Recent werd een nieuwe classificatie voor complicaties die op kunnen treden bij (her)operaties ontwikkeld, ClassIntra®. Deze score is gevalideerd in een multicenterstudie waaraan het Radboudumc deelnam. In deze studie werd niet gekeken naar de verschillende types complicaties, bijvoorbeeld een onbedoeld darmletsel door adhesiolyse. Bovendien werd de overeenstemming tussen verschillende beoordelaars over wat en hoe ernstig een peroperatieve complicatie was, bepaald op grond van een beperkt aantal fictieve casussen in plaats van op praktijkvoorbeelden. In **hoofdstuk 6** werd met behulp van eerder prospectief verzamelde gedetailleerde data uit de LAPAD studie over het optreden van complicaties tijdens een geplande buikoperatie en het optreden van postoperatieve complicaties, gekeken naar de overeenstemming tussen verschillende beoordelaars van de

ClassIntra®. Ook werd de voorspellende waarde onderzocht van de hoogste ClassIntra® score op het voorkomen van postoperatieve complicaties. In het totaal werden data bekeken van 755 buikoperaties. Twee teams scoorden voor elke operatie de complicaties volgens de ClassIntra®. Analyse toonde een goede overeenkomst in ClassIntra® scores tussen beide teams. Adhesiolyse was een van de drie sterkste voorspellers voor postoperatieve complicaties (OR 6,17; 95% BI 2,91 - 9,44). Andere voorspellers van postoperatieve complicaties waren bloedingen tijdens de operatie en beschadiging aan andere organen. De bevestiging van het verband tussen aan adhesiolyse gerelateerde complicaties tijdens een operatie en de postoperatieve complicaties, heeft belangrijke klinische implicaties voor de directe postoperatieve zorg. Resultaten van deze studie benadrukken het belang om een groter bewustzijn te creëren met betrekking tot de kennis van de adhesie-gerelateerde ziektelast. Hierdoor zal ook het draagvlak toenemen voor het ontwikkelen en toepassen van aanvullende strategieën om adhesies te voorkomen.

Door de hoge incidentie van de adhesie-gerelateerde postoperatieve complicaties, hebben adhesies ook aanzienlijke financiële gevolgen voor de gezondheidszorg. Eerdere schattingen van de kosten voor een opname voor strengileus zijn inmiddels verouderd en grotendeels gebaseerd op niet uniforme prijsafspraken tussen ziekenhuizen en fabrikanten en/of verzekeraars. Het gebrek aan een goed inzicht in de kosten belemmert de implementatie van strategieën om adhesies te verminderen. **Hoofdstuk 7** geeft een gedetailleerde schatting van de kosten die gepaard gaan met een opname voor strengileus. Over een periode van twee jaar werden alle opnames gescreend voor patiënten met de diagnose strengileus in het Radboudumc. In het totaal waren er 39 patiënten die voldeden aan de inclusiecriteria. Van deze patiënten werd 49% operatief behandeld. De gemiddelde opnameduur voor een patiënt met een operatieve behandelde strengileus was zestien dagen, vergeleken met vier dagen voor een niet-operatief behandelde patiënt met een strengileus. De ziekenhuiskosten voor een operatief behandeling bedroegen € 16.305, tegenover € 2.277 voor een behandeling zonder operatie. De resultaten in dit hoofdstuk vormden een belangrijke basis voor het opzetten van een vervolgstudie naar de kosteneffectiviteit van adhesiereductiestrategieën. In **hoofdstuk 8** werd een model gepresenteerd voor het routinematig gebruik van adhesiebarriers bij patiënten met een

hoog risico op adhesie-gerelateerde klachten, namelijk zij die een colorectale operatie ondergaan. In het model werd gekeken naar de 4-jaars kans op het ontwikkelen van adhesie-gerelateerde problematiek, gedefinieerd als een strengileus of problemen bij heroperaties. Verschillende online zoeksystemen werden gebruikt om de relevante gegevens in de literatuur te vinden voor de kansberekeningen in dit model. Hierbij werden gewogen kansen bepaald voor de verschillende mogelijke gebeurtenissen in het model. Het model toonde aan dat het routinematig gebruik van een adhesiebarrier na colorectale kijkoperaties de kans op adhesie-gerelateerde complicaties effectief vermindert tegen een geringe stijging van de kosten. Maatschappelijke kosten voor de behandeling van strengileus waren in dit onderzoek niet meegenomen. We beschouwden de geringe stijging van de directe zorgkosten als verwaarloosbaar in vergelijking met de verwachte maatschappelijke besparingen. We concludeerden dat het gebruik van adhesiebarriers in patiënten met een hoog risico op adhesie-gerelateerde problemen kosteneffectief is.



# Appendices

Dankwoord
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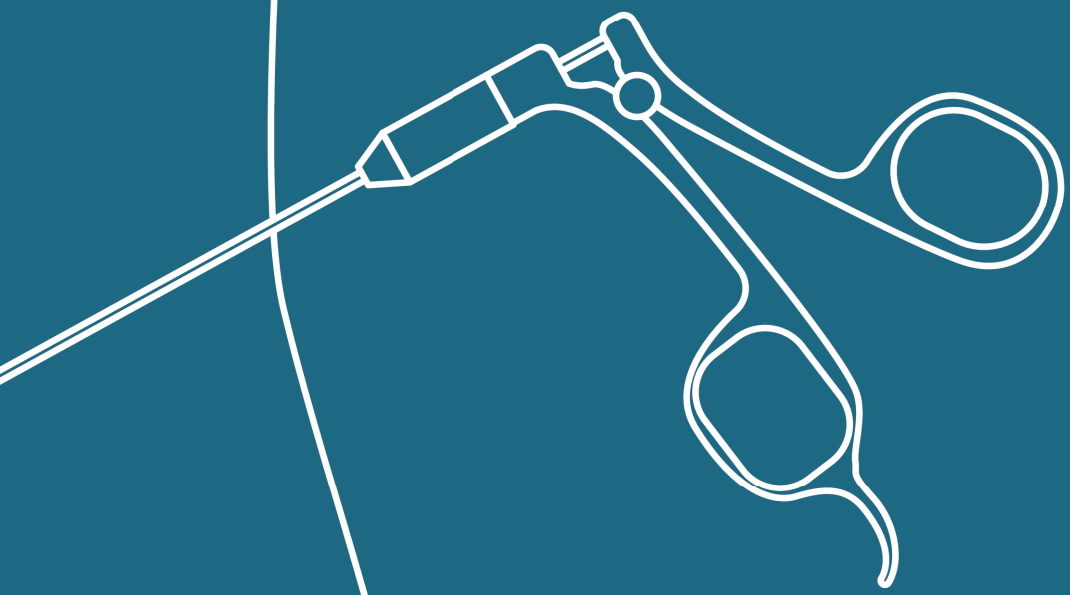

## Dankwoord

Het dankwoord, het leukste, meest gelezen en misschien ook wel het moeilijkste deel van dit proefschrift om te schrijven. Enkele jaren geleden begon ik aan dit project om mij verder te verdiepen in het wetenschappelijke veld van de chirurgie, meer specifiek in de verklevingen (adhesies). Zoals het woord misschien al verraadt, zodra je er eenmaal aan vast zit, kom je er niet meer zo makkelijk van los. Terugkijkend, zie ik een periode waarin ik heel veel geleerd heb. Achteraf kan ik zeggen: “het was het allemaal waard!” Toch blijft er bij mij één vraag hangen: “wat doet een normaal mens eigenlijk met al zijn vrije tijd?”

Beste Harry, je ogen altijd op de horizon, waar ik bezig was de grond voor mijn voeten te ontdekken, was jij al bezig met wat er daarna ging komen en hoe dit paste in een groter geheel. Jij wist met je kritische vragen en creatieve geest alle projecten samen te brengen en een duidelijke lijn te geven aan het geheel. Door prikkelende vragen te stellen daagde je me uit om verder te denken dan alleen de getallen die SPSS produceerde. Hoe stonden deze getallen in verhouding met de kennis die we al hadden en wat voegde dit toe aan het klinisch vraagstuk. Als promoveren een schip was, stond jij in het kraaiennest met de verrekijker. Dank, zonder jou was dit schip mogelijk al gezonken.

Beste Richard, je gedrevenheid en analytisch vermogen blijven me na al die jaren dat ik je nu ken nog steeds verbazen. Ik heb enorme waardering voor de manier waarop jij alle ballen in de lucht houdt. Je hebt me enthousiast weten te krijgen voor dit onderwerp met de passie die jij hebt voor adhesies. Jouw begeleiding heeft ervoor gezorgd dat ik lastige statistische en klinische vragenstukken op een gestructureerde manier kan analyseren. Dank voor alle tijd en moeite die je in dit project hebt gestoken.

Beste Martijn, het doet me toch een beetje pijn dat het stroomschema uit hoofdstuk 8 dat we op A2 uitgetekend hadden, niet langer de deur van je werkkamer versiert. Vaak hebben we hier samen naar gekeken om het lastige statistische stuk helder te krijgen. Het ging pas van de deur af zodra we het stuk gepubliceerd hadden. En wat blijkt ook hier, de aanhouder wint. Dank voor je relativeringsvermogen en humor. Daar waar Richard en ik soms wat door

konden draven in het statistische geneuzel, bracht jij ons weer terug bij de kern van het klinische probleem.

Beste leden van de manuscriptcommissie, prof. Meijerink, prof. Rovers & prof. Lange, dank voor de tijd en aandacht die jullie hebben gestoken in het beoordelen van mijn proefschrift. Alle leden van de commissie, dank voor het deelnemen aan de oppositie.

Dank aan alle coauteurs voor jullie kritische blik en ondersteuning in het schrijven van de verschillende artikelen.

To all international collaborators: thank you for your support and for critically reviewing the manuscripts. I hope that this pleasant collaboration will result in more highly relevant research papers.

Alle collega's uit het Canisius Wilhelmina Ziekenhuis bedankt voor de afgelopen twee gezellige en leerzame jaren. Dank voor de fijne samenwerking. Ik hoop dat we nog vele jaren als collega's samen mogen werken. Laten we vooral ook de feestjes en sportieve activiteiten voortzetten!

(oud-)Collega's uit het Radboud, dank voor de jaren die we samen hebben gewerkt. Bijzonder bedankt voor de mogelijkheden die ik hier gekregen heb om mezelf niet alleen verder te ontwikkelen als arts, maar ook als docent en onderzoeker.

Beste Mark & Marjolein, Thomas & Renée, Fleur & Rens, Ran, Duco & Lotte, Floris & Josine, Anke & Wytse, wie had ooit gedacht dat we hier zouden staan, ik in ieder geval niet! Kleine meisjes en jongens worden groot. Roadtrips, vakanties, weekendjes weg, stapavonden, kerstdiners, festivals, spelletjesavonden en nog veel meer, waren voor mij de hoogtepunten uit afgelopen jaren. Dank voor de steun op alle serieuze momenten maar bijzonder dank voor het creëren van vele niet-al-te-serieuze momenten. Dat er nog heel veel niet-al-te-serieuze momenten mogen komen!

Ik kan helaas niet iedereen bij naam noemen, dan zou dit proefschrift twee keer zo dik worden. Voor iedereen die met drankjes, spelletjes, gezelligheid en etentjes mijn afgelopen jaren leuker heeft gemaakt, dank, en laten we zorgen dat dit nog vele jaren doorgaat.

Lieve pap en mam, niet altijd had ik zin om de vragen te beantwoorden: hoe staat het er nu voor met je proefschrift? Heb je nog iets gepubliceerd? Nu dit project zijn einde heeft bereikt, wordt het misschien ook wat makkelijker om uit te leggen wat ik al die jaren heb gedaan. Ik bereid me vast voor op de vragen die nu komen gaan aan de hand van wat jullie lezen in dit proefschrift, die ik natuurlijk van harte wil beantwoorden. Dank voor jullie ondersteuning en positieve bekrachtiging.

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Liefste Saar, eindelijk is het klaar! Dit zal voor ons beiden als muziek in de oren klinken. Je hebt vaak een luisterend oor moeten bieden aan mijn gezeur over dingen die niet liepen zoals ik zou willen dat ze liepen. Je kon me er ook goed op wijzen, dat het soms even genoeg was en dat het nu tijd was voor ontspanning. Nu dit project af is, beloof ik dat ik hier meer tijd voor heb. Zonder jouw steun en vertrouwen stond ik hier nu niet. Je bent mijn steun geweest in al deze jaren en hopelijk nog in alle jaren die volgen.

## Curriculum Vitae

Pepijn Krielen was born on July 7th, 1990 in Malden the Netherlands as the oldest of three siblings. After graduating from the Nijmeegse Scholengemeenschap Groenewoud in Nijmegen he started his study Biomedical Sciences on the Radboud University. After completing his Bachelor of Science degree he switched to Medicine. During his internships he developed a strong affinity for the academic field of surgery. He started as a research student in the field of adhesions at the department of surgery of the Radboud University Medical Center. After graduating in November 2016 he started as surgical resident (ANIOS) at the Radboud University Medical Center. He developed an urge to teach medical students several aspects of the surgical working field. Together with the Radboud Health Academy (RHA) and the Hogeschool Arnhem Nijmegen (HAN) he developed an interprofessional acute health care training. He started his thesis on abdominal adhesions and adhesive small bowel obstruction on the 1st of January 2017 under the supervision of prof. H. van Goor, Dr. M.W.J. Stommel and Dr. R.P.G. ten Broek at the Radboud University Medical Center. During his time as PhD candidate he presented the results of his research on several national and international meetings. On the 1st of January 2019 he started as surgical resident (ANIOS) at the Canisius Wilhelmina Hospital in Nijmegen. During his clinical duties he finalized his PhD thesis. He will start as a surgical resident at the beginning of 2021. He is pursuing a career in surgery, combined with teaching and research responsibilities.

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* Both authors contributed equally

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* Both authors contributed equally

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## Data Management Summary

Data obtained during the construction of this thesis was archived according to the Findable, Accessible, Interoperable an Reusable (FAIR) principles. The SCAR update and SCAR colorectal update studies (chapter 2 & 3) used data from the Scottish Medical Record Linkage Database, managed by the Information and Statistics Division of the National Health Service (NHS) Scotland. This database contains records from 1981 onwards for all Scottish inpatient and daycare hospital admissions, excluding psychiatric or maternity admissions. Follow-up of individual patients' readmissions is included in this database. Data from the NHS database are annually validated at hospital level. For research purposes we requested necessary data from the NHS. Variables were coded using publicly available classification systems, e.g. ICD-10 and OPCS-4 codes. Accessing the data was only possible via an approved network after a double step verification. Data were made available for analysis during a year after the start of both studies.

All existing (meta)data files of chapter 4-8 were digitally stored in a structured and logical manner on a local server of the department of surgery of the Radboud university medical center (H:\COMMON\Krielen). Servers were centrally backed-up on a regular basis. Data files were accessible by the appropriate members of the research group. Codebooks were documented, describing all (meta)data in detail. To prevent errors in the data, all saved files were provided with the date of the last editing of the data. Using this system, previous versions could always be accessed to check potential errors. All data can be requested through the appropriate members of the department of surgery of the Radboudumc upon reasonable request.

The review in chapter 6 was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol of this systematic review and meta-analysis has been registered on PROSPERO CRD42018107087 (http://www.crd.york.ac.uk/prospero). Data were analyzed using Review Manager (RevMan).

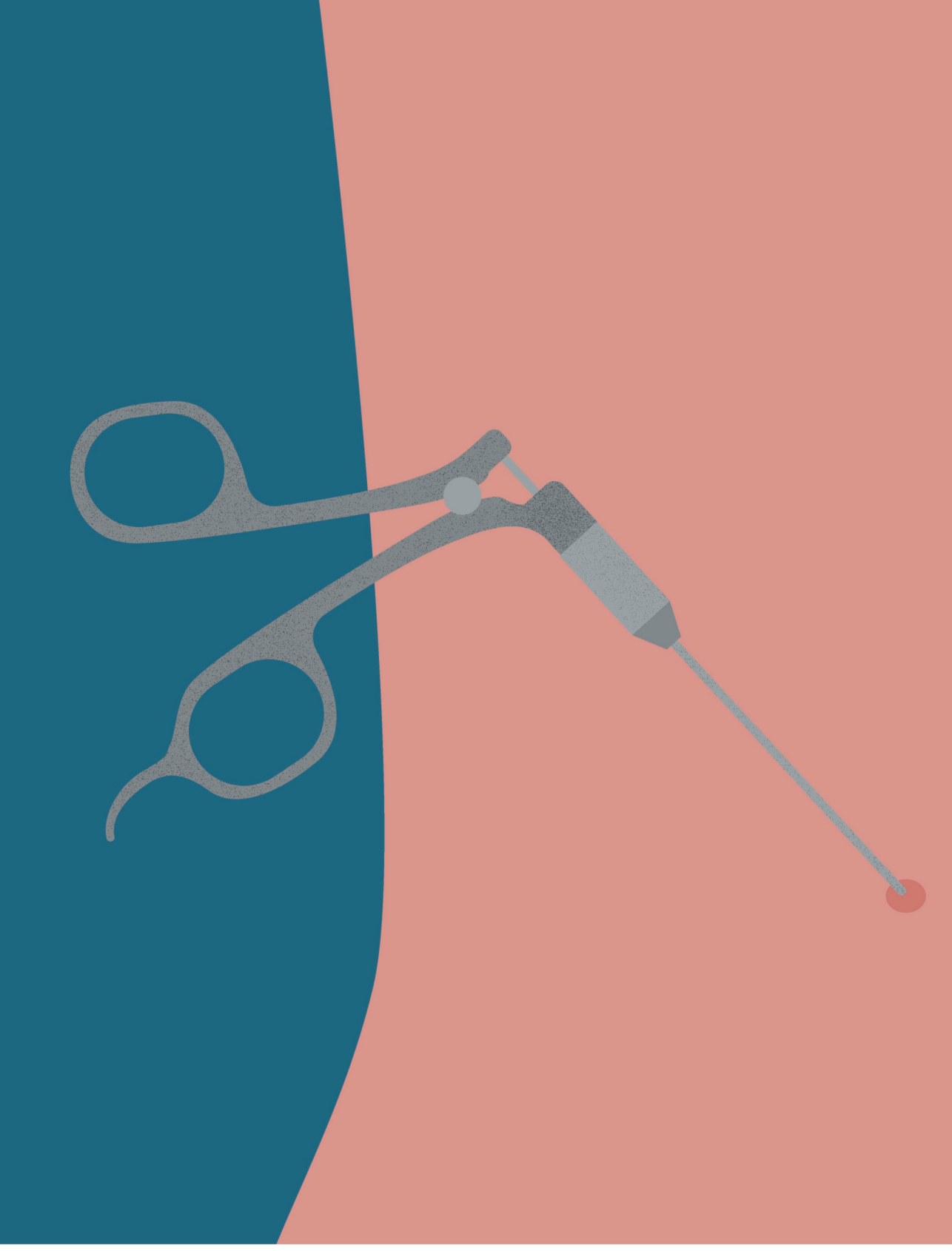
All data generated and collected for this thesis, with the exclusion of data for chapter 2 & 3, will be saved for 15 years after termination of the research (December 1st, 2020).

# PhD Portfolio

Institute for Health Sciences
Radboudumc

| | | | |
|---|---|---|---|
| **Name PhD candidate** | Pepijn Krielen | **PhD period** | 01-01-2017 – 11-02-2020 |
| **Department** | Surgery | **Promotor** | Prof. H. van Goor |
| **Graduate School** | Radboud Institute for Health Sciences | **Co-promotors** | Dr. R.P.G. ten Broek<br>Dr. M.W.J. Stommel |

| | Year(s) | ECTS |
|---|---|---|
| **TRAINING ACTIVITIES** | | |
| **a) Courses & Workshops** | | |
| - Graduate School specific introductory course (RIHS) | 2018 | 1.0 |
| - Education in a Nutshell | 2018 | 1.0 |
| - eBROK course | 2018 | 1.5 |
| - Opleiden van coassistenten in de praktijk | 2018 | 1.0 |
| - Topclass Medisch Onderwijs | 2019 | 4.0 |
| - Scientific Integrity | 2020 | 0.5 |
| **b) Symposia & congresses** | | |
| - World Society of Emergency Surgery congress, Dublin (IE), oral presentation | 2016 | 1.5 |
| - European Society of Gastrointestinal Endoscopy, anti-adhesions in gynaecology expert group (ANGEL) meeting, Vienna (AU), oral presentation | 2018 | 1.5 |
| - Digestive Disease Days, Veldhoven (NL), oral presentation | 2018 | 1.0 |
| - Academic Surgical Congress, Texas (US), 2x oral presentation | 2019 | 3.0 |
| - Chirurgendangen, Veldhoven (NL), 2x oral presentation | 2019 | 1.0 |
| - World Society of Emergency Surgery congress, Nijmegen (NL), oral presentation | 2019 | 3.0 |
| **TEACHING ACTIVITIES** | | |
| **c) Lecturing** | | |
| - Simulated acute health care training (Master Medicine) | 2017/18/19/20 | 3.0 |
| - Suture Techniques (Master Medicine) | 2017/18 | 1.0 |
| **d) Supervision of internships** | | |
| - Supervision master student internships | 2016/17 | 2.0 |
| - Supervision bachelor student internships | 2017/18 | 4.0 |
| - Supervision elective bachelor student internships | 2019/20 | 4.0 |
| **Total** | | **34.0** |



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